HEALTH TECHNOLOGY ASSESSMENT REPORT
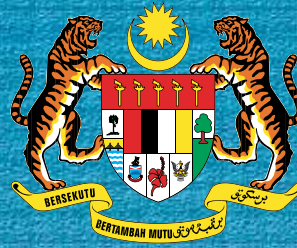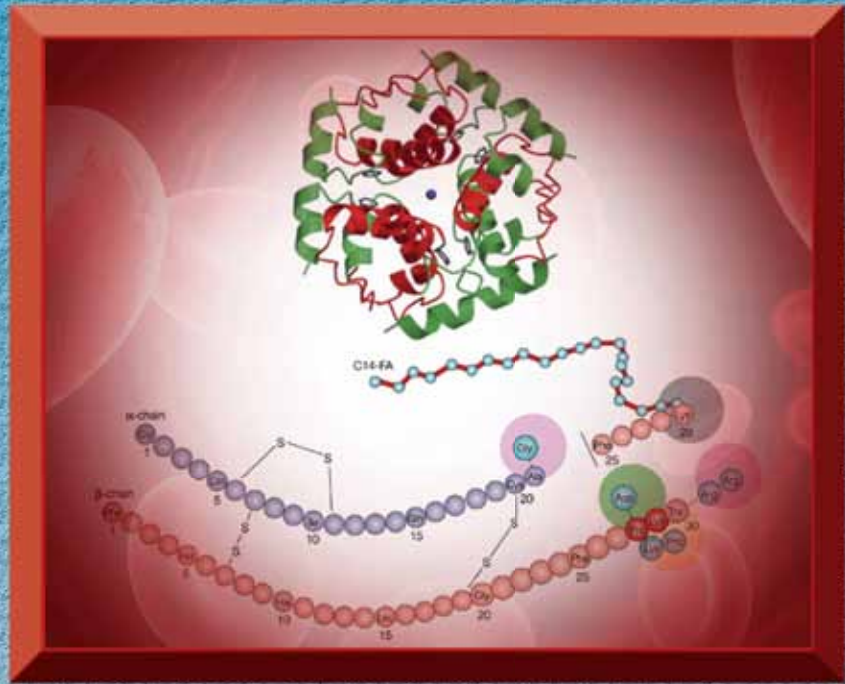
MINISTRY OF HEALTH MALAYSIA

INSULIN ANALOGUES

MaHTAS

Malaysian Health Technology Assessment Section

**MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH MALAYSIA**

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Health Technology Assessment Report

INSULIN ANALOGUES

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DISCLOSURE

EXECUTIVE SUMMARY

Background

Diabetes mellitus still remains one of the most significant causes of morbidity and mortality in the world, and its global impact is likely to accelerate over the coming decades. The goal of diabetic treatment is to achieve tight glucose control, avoid chronic complications and limit hypoglycaemic episodes frequency in everyday life with minimal weight gain. Success with insulin management ultimately depends on how closely a given regimen can mimic normal physiologic insulin release patterns. The new insulin analogues have been designed to more closely mimic physiologic insulin profiles. However, the cost of insulin analogues is more expensive than conventional human Insulin.

Technical features

The newer insulin analogues have several improvements due to their modified action profile. It is claimed that the main advantages of rapid-acting preparations include faster onset of action and shorter duration of action. Long-acting analogues afford structural changes, which delay the onset of action, allow slow and continuous absorption into the systemic circulation and prolong the duration of action. Thus, producing a time-concentration profiles, imitates the normal insulin basal level and leads to physiological basal glycaemic control with less nocturnal hypoglycaemia. There are three commercially available rapid-acting insulin analogues: insulin lispro, insulin aspart and insulin glulisine. There are two long-acting insulin analogues: insulin glargine and insulin detemir. Three types of fixed-ratio insulin analogues mixes are currently available: a 75% insulin lispro protamine suspension with 25% insulin lispro, a 50% insulin lispro protamine suspension with 50% insulin lispro, a 70% insulin aspart protamine suspension with 30% insulin aspart. These formulations have been developed to minimise the errors that can occur when patients self-mix insulin combinations. The new insulin analogues can be administered at mealtimes while conventional human insulin is recommended to be administered roughly 30 minutes prior to eating.

Policy question

In Ministry of Health facilities, should insulin analogues be used for all diabetic patients treated with insulin?

Objective

To assess the safety, efficacy or effectiveness and economic implications of using rapid-acting, long-acting or premixed insulin analogues compared with conventional human insulin for treatment of type 1, type 2, or gestational diabetes mellitus.

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R), EBM Reviews-Cochrane Database of Systematic Reviews, EBM Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews–Database of Abstracts of Review of Effects, EBM Reviews-Health Technology Assessment, EBM Reviews-NHS Economic Evaluation Database and PubMed. No limits were applied to the search, except for publication year from 2006 to current for EBM Reviews-Cochrane Central Register of Controlled Trials. Other database searched include FDA database. The last search was run on 7 March 2012. Additional articles were identified from reviewing the references of retrieved articles and contacting the authors. Studies were selected based on inclusion and exclusion criteria. All relevant literature was appraised using the Critical Appraisal Skills Programme (CASP) tool for systematic review (including HTA reports) and economic evaluation and Jadad scale for RCT. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

Results and conclusion

A total of 878 abstracts were screened using the inclusion and exclusion criteria. After reading, appraising and applying the inclusion and exclusion criteria to 172 full text articles, 45 full text articles were included. The 45 full text articles finally selected for this review comprised of five HTA reports, 10 systematic reviews, 16 RCTs, 13 cost-effectiveness analyses and one costing analysis.

Efficacy or Effectiveness of Insulin Analogues
Rapid-acting insulin analogues

- There was good level of evidence to suggest that treatment with insulin lispro or insulin aspart compared with regular human insulin resulted in small but significantly lower HbA1c values (ranged between 0.09% and 0.14%) in adults with type 1 diabetes mellitus, but not in children.

- The HbA1c values were found to be comparable for the two treatment groups in type 2 diabetes mellitus, gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus. Postprandial blood glucose was also found to be significantly lower in groups treated with insulin lispro or insulin aspart compared with regular human insulin (ranged between 0.83 mmol/L and 1.43 mmol/L). However, fasting and preprandial blood glucose was similar for both treatment groups.

- There was evidence to suggest greater treatment satisfaction in type 1 diabetes mellitus and in pregnant women with type 1 diabetes mellitus treated with insulin lispro or insulin aspart compared with regular human insulin.

Long-acting insulin analogues

- There was good level of evidence to suggest that treatment with insulin glargine compared with NPH insulin resulted in small but significantly lower HbA1c level by 0.11% in adults with type 1 diabetes mellitus but not in children and adolescents or patients with type 2 diabetes mellitus. Fasting plasma glucose was found to be significantly lower in type 1 diabetes mellitus treated with insulin glargine or insulin detemir (ranged between 0.87 mmol/L and 1.01 mmol/L), while postprandial blood glucose was found to be significantly lower in type 2 diabetes mellitus treated with insulin glargine compared with NPH insulin.

- For type 1 and type 2 diabetes mellitus, there was evidence to suggest that quality of life and treatment satisfaction was greater with insulin glargine compared with NPH insulin.

- There was fair to good level of evidence to suggest that treatment with insulin detemir was associated with smaller weight gain in children and adults with type 1 diabetes mellitus and in type 2 diabetes mellitus compared with NPH insulin.

Premixed insulin analogues

- There was good level of evidence to suggest that treatment with premixed insulin analogues had similar effect in lowering HbA1c but significantly reduced postprandial blood glucose in type 1 and type 2 diabetes mellitus [ranged between 17.8 mg/dL (0.98 mmol/L) and 30.0 mg/dL (1.68 mmol/L)] compared with premixed human insulin.

Safety
Rapid-acting insulin analogues

- There was good level of evidence to suggest that when compared with regular human insulin, the use of insulin lispro resulted in lower risk for nocturnal hypoglycaemia in adults and adolescents with type 1 diabetes mellitus (reduction by 49% and 39% respectively) and also in type 2 diabetes mellitus in some studies.

- The risk for severe hypoglycaemia was also lower in adult with type 1 diabetes mellitus by 20%.

- Similarly, treatment with insulin aspart resulted in lower risk for nocturnal hypoglycaemia (reduction between 33% and 45%) in type 1 diabetes mellitus.

- There was fair to good level of evidence to suggest that the frequency and type of adverse events were similar between rapid-acting insulin analogues and regular human insulin.

Long-acting insulin analogues

- There was good level of evidence to suggest that there were similar risk for overall, severe and nocturnal hypoglycaemia for type 1 diabetes mellitus treated with insulin glargine compared with NPH insulin.

- In patients with type 2 diabetes mellitus, the risk for nocturnal and overall hypoglycaemia was significantly lower in patients treated with insulin glargine compared with NPH insulin by 34% to 46% and 11% respectively. Five people with type 2 diabetes mellitus needed to use once-daily morning glargine rather than once-daily evening NPH, while eight people with type 2 diabetes needed to use once-daily evening glargine rather than once-daily evening NPH to avoid one person from experiencing a nocturnal symptomatic hypoglycaemic event.

- There was good and fair level of evidence to suggest similar foetal and neonatal outcomes and progression of diabetic retinopathy in patients treated with insulin glargine compared with NPH insulin.

- There was good level of evidence to suggest that treatment with insulin detemir compared with NPH insulin resulted in lower risk for nocturnal hypoglycaemia in type 1 diabetes mellitus (adult, children and adolescents) by 8% to 15%, while severe hypoglycaemia was found to be lower in adult with type 1 diabetes mellitus by 25% to 34%.

- Type 2 diabetes mellitus treated with insulin detemir was found to have significantly lower risk for nocturnal and overall hypoglycaemia (reduction by 34% to 47% and 18% to 32%, respectively).

Premixed insulin analogues

- There was good level of evidence to suggest that the risk for hypoglycaemia was similar for premixed insulin analogues and premixed human insulin.

Cost / cost-effectiveness / economic evaluation

- Studies of incremental cost-effectiveness ratio per quality adjusted life year gained generally demonstrated that insulin analogues could be cost-effective compared with conventional human insulin. The drug costs were higher in the insulin analogues group than the conventional human insulin, but this was partly offset by reduced complication costs.

Recommendation

Based on the above review, treatment with insulin analogues compared with conventional human insulin appeared to offer minor benefit in terms of glycaemic control as reflected in HbA1c level, postprandial blood glucose and fasting blood glucose but have advantages in terms of reduced occurrence of hypoglycaemia, particularly nocturnal hypoglycaemia and severe hypoglycaemia as reported in some studies. While the adverse events (excluding hypoglycaemia episodes) were found to be similar in both treatment groups, patients treated with insulin analogues showed greater treatment satisfaction and less weight gain. Hence, it is recommended that insulin analogues should be made available for treatment of all type 1 diabetes mellitus and for type 2 diabetes mellitus who have recurrent hypoglycaemia. However, it is not recommended for gestational diabetes mellitus. More high quality clinical trials are warranted to provide evidence on long term safety and effectiveness of insulin analogues. Although insulin analogues could be considered cost-effective in some countries, generalizability and international comparisons of economic evaluations are limited. Local cost analyses research with the decision maker and societal perspective are encouraged. The price of insulin analogues in Malaysia is much higher compared with conventional human insulin. From literature review, we observed that there were price variations across countries and regions of the world. Hence, we need to negotiate for better pricing package.

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ABBREVIATIONS

DM	Diabetes Mellitus
IA	Insulin analogues
USD	United States Dollar
WHO	World Health Organization
ID	International Dollars (ID)
U.S.A.	United States of America
U.K.	United Kingdom
DCCT	Diabetes Control and Complications Trial
UKPDS	United Kingdom Prospective Diabetes Study
U.S. FDA	United States and Drug Administration
ILis	Insulin Lispro
IAsp	Insulin Aspart
IGlar	Insulin glargine
IDet	Insulin detemir
BiAsp 30	Premixed insulin aspart 30
BHI 30	Premixed human insulin 30
RHI	Regular human insulin
NPH	Neutral Protamine Hagedorn
OADs	Oral antidiabetics
WMD	Weighted mean difference
CI	Confidence interval
SMD	Standardized mean difference
MD	Mean difference
SD	Standard deviation
SE	Standard error
NNT	Number needed to treat
ICER	Incremental cost-effectiveness ratio
QALY	Quality adjusted life years
DTSQ	Diabetes Treatment Satisfaction questionnaire
WED	Well-being Enquiry for Diabetes (WED) questionnaire
AWI	Average weighted impact
QoL	Quality of life
DSQOLS	Diabetes-specific quality of life scale
WBQ	Well-being questionnaire
ADDQOL	Audit of Diabetes Dependent Quality of Life Questionnaire
FBG	Fasting blood glucose
MDBG	Mean daily blood glucose
CV	Coefficient of variation
MAGE	Mean amplitude of glycaemic excursion
BMI	Body Mass Index
Kg	Kilogram
ETDRS	Early Treatment Diabetic Retinopathy Study
TEAEs	Treatment-emergent adverse events

HEALTH TECHNOLOGY ASSESSMENT
INSULIN ANALOGUES

1.   BACKGROUND

Diabetes mellitus still remains one of the most significant causes of morbidity and mortality in the world, and its global impact is likely to accelerate over the coming decades. According to the World Health Organization (WHO), 346 million people worldwide have diabetes and more than 80% of diabetes deaths occur in low-and middle income countries. The WHO projects that diabetes deaths will double between 2005 and 2030.[1] The global health expenditure on diabetes is expected to total at least United States Dollars (USD) 376 billion or International Dollars (ID) 418 billion in 2010 and USD 490 billion or ID 561 billion in 2030.[2] The WHO defines diabetes mellitus as "a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both".[3] There are two main types of diabetes: Type 1 diabetes usually develops in childhood and adolescence and patients require lifelong insulin injections for survival. Type 2 diabetes usually develops in adulthood and is related to obesity, lack of physical activity, and unhealthy diets. This is the more common type of diabetes (representing 90% of diabetic cases worldwide) and treatment may involve lifestyle changes and weight loss alone, or oral medications or even insulin injections. Other categories of diabetes include gestational diabetes (a state of hyperglycaemia which develops during pregnancy) and other rare causes (genetic syndromes, acquired processes such as pancreatitis, diseases such as cystic fibrosis, exposure to certain drugs, viruses, and unknown causes).[3]

In the short term, hyperglycaemia causes symptoms of increased thirst, increased urination, increased hunger, and weight loss. However, in the long-term, it causes microvascular and macrovascular complications. Microvascular complications include diabetic retinopathy leading to blindness, nephropathy leading to renal failure, neuropathy leading to impotence and diabetic foot disorders. Macrovascular complications include cardiovascular diseases such as heart attacks, strokes and insufficiency in blood flow to the legs.[3,4,5] In addition, the risk of tuberculosis is three times higher among people with diabetes.[6]

According to the WHO Global Status Report on noncommunicable diseases 2010, the global prevalence of diabetes in 2008 was estimated to be 10% in adults aged 25 years and above. The prevalence of diabetes was highest in the Eastern Mediterranean Region and the Region of the Americas (11% for both sexes) and lowest in the WHO European and Western Pacific Regions (9% for both sexes).[7] According to the Malaysian National Health and Morbidity Survey III, in 2006 the overall prevalence of diabetes mellitus among adults aged 18 years and above was 11.6%. The Indians had the highest prevalence of 19.9%, followed by Malays 11.9% and Chinese 11.4%. It was reported that 4.3% of patients with known diabetes had amputation, 3.4% had suffered a stroke event and 1.6% was on some form of renal replacement therapy. Usage of insulin alone or in combinations was low at 7.2% of patients.[8] A more recent Malaysian National Health and Morbidity Survey 2011, reported an increased in the overall prevalence of diabetes mellitus to 15.2%. The prevalence was highest among those in the 65 to 69 years age group and was lowest in the 18 to 19 years age group. Similar to the result of the survey conducted in 2006, the prevalence was highest in Indians (24.9%), followed by the Malays (16.9%) and Chinese (13.8%). Among the known diabetes, 19.3% claimed that they were on insulin therapy, 79.9% claimed to be on oral anti-diabetic drugs within the past two weeks and 0.2% opted for traditional and complementary medicine.[9]

Zhang *et al.* in their report on global healthcare expenditure on diabetes among adults aged 20 to 79 for 2010 and 2030 mentioned that there was a large disparity in total health spending for diabetes among the top 80 most populous countries, varying from USD 1.3 million to USD 198.0 billion. The country with the highest total expenditure, the United States of America (U.S.A.) will spend 52.7% of global expenditure, while India, the country with the largest population of people living with diabetes will spend an estimated USD 2.8 billion or less than 1% of the world total. The global health expenditure for diabetes in 2030 will be larger (30% to 40%) than those of 2010 and the rate of growth in diabetes expenditure will vary by region. They reported that the health expenditure for diabetes for 2010 in Malaysia was estimated between USD 600,407,000.75 and USD 1,005,095,000.05 (16% of the health expenditure). The mean health expenditure per person with diabetes in 2010 was USD 325.24. It is estimated that in 2030, the health expenditure for diabetes will increase to between USD 1,073,139,000.00 and USD 1,828,693,000.40.[2]

Two clinical studies, the Diabetes Control and Complications Trial (DCCT) among type 1 diabetes and the United Kingdom Prospective Diabetes Study (UKPDS) among type 2 diabetes published in 1993, 1998, 2000 and 2008 demonstrated that intensive control of serum glucose levels can minimize the development of diabetes-related complications.[10-13] In the DCCT trial, intensive therapy effectively delays the onset and slows the progression of diabetic retinopathy, nephropathy and neuropathy in patients with insulin dependent diabetes mellitus (IDDM). However, the major adverse event associated with intensive insulin therapy was a two-to-threefold increase in severe hypoglycaemia.[10] In the UKPDS, each 1% reduction in mean HbA1c was associated with reductions in risk of 21% for any end point related to diabetes, 21% for deaths related to diabetes, 14% for myocardial infarction and 37% for microvascular complications. There was no indication of a threshold for any complication below which the risk is no longer decrease nor a level above which risk is no longer increased. The authors concluded that any reduction in HbA1c is likely to reduce the risk of complications, with the lowest risk being in those with HbA1c values in the normal range.[12] Similar to the DCCT, the rates of major hypoglycaemic episodes and weight gain were higher in the insulin group.[11]

Malaysian Ministry of Health Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus (4th Edition) 2009, recommended that therapy for most patients with type 2 diabetes mellitus should be targeted to achieve a HbAlc of less than 6.5%.[14] Thus, the goal of diabetic treatment is to achieve tight glucose control, avoid chronic complications and limit hypoglycaemic episodes frequency in everyday life with minimal weight gain. Therefore, physicians and patients should strive to mimic, as closely as possible, the serum level of insulin produced in a healthy person.[15] In reality, it is difficult to obtain and maintain near normal concentrations of HbA1c in patients with type 2 diabetes, particularly in those with high concentration of HbA1c at diagnosis of diabetes. Intensification of treatment by adding insulin to improve the relatively modest reduction in glycaemia achieved with oral hypoglycaemia can be constrained by reluctance from patients and providers, partly because of side effects such as hypoglycaemia and weight gain.[12]

Success with insulin management ultimately depends on how closely a given regimen can mimic normal physiologic insulin release patterns.[15] Human insulin (conventional insulin) is synthetic insulin which is laboratory created by growing insulin proteins within *Escherichia coli* to mimic the insulin in humans. It is available in two forms: a short acting (regular) form and an intermediate acting [Neutral Protamine Hagedorn (NPH)] form.[16] While management of diabetes has greatly improved in recent years with newer strategies focusing on aggressive glucose control, it is claimed that the conventional human insulin products have fallen short of providing optimal therapy. The new insulin analogues (IA) including rapid-acting insulin analogues, the long-acting basal insulin analogues and premixed insulin analogues formulations have been designed to more closely mimic physiologic insulin profiles through improved pharmacokinetic characteristics, which result in either more rapid or prolonged pharmacodynamic effects.[15]

Rapid-acting also known as short-acting insulin analogues are designed to offer a more rapid onset of action and shorter duration of activity than regular human insulin. Currently, there are three commercially available rapid-acting insulin analogues: insulin aspart, insulin lispro and insulin glulisine. It can be administered at mealtimes and produce a rapid and short-lived insulin spike to address postprandial glucose elevations. This imparts a significant advantage in convenience for patients relative to human insulin, which is recommended to be administered roughly 30 minutes prior to eating. There are currently two long-acting basal insulin analogues preparations available: insulin glargine and insulin detemir which have been designed to approach the ideal characteristics of basal insulin by having a relatively flat, 24-hour basal insulin supply, with less variability in action compared to human NPH insulin. Three types of fixed-ratio insulin analogues mixes are currently available: a 75% insulin lispro protamine suspension with 25% insulin lispro, a 50% insulin lispro protamine suspension with 50% insulin lispro, a 70% insulin aspart protamine suspension with 30% insulin aspart. These formulations have been developed to minimise the errors that can occur when patients self-mix insulin combinations.[15]

Despite these clear pharmacologic advantages, measurable clinical benefits in a complex disease such as diabetes can be hard to measure. Several systematic reviews and health technology assessments (HTAs) have evaluated the clinical efficacy and safety of insulin analogues. While some reviews showed statistically significant improvement in glycaemic control compared to regular human insulin. However, there were still uncertainty regarding their optimal use or their long term efficacy or effectiveness, safety, and cost-effectiveness.[17-20] Over the last decade, the use of human insulin has declined from being the sole type of insulin used, representing about one-third in high income countries and two-thirds in middle income countries by 2009. In low-income countries, human insulin still comprised over 94% of all insulin. Decreasing proportionate use of human insulin was mirrored by rising proportions of analogue insulin, increasing to two-thirds of all insulin in high income countries in 2009, with middle-and-low income countries following behind. In low-income countries, however, analogue insulin still represented a median of only 4% of insulin usage by 2009.[21]

In Malaysia, the use of insulin analogues in public hospitals range from 2% to 3%. This is because insulin analogues are more expensive (three to five times) than conventional human insulin. Because health care resources are limited, there is a need to determine if insulin analogues are justified for all or some diabetic groups. This HTA was requested by the Head of Endocrinology Services, Ministry of Health.

2. TECHNICAL FEATURES

Insulin is a polypeptide hormone that controls the storage and metabolism of carbohydrates, proteins, and fats. The activity occurs primarily in the liver, in muscle, and adipose tissues after binding of insulin molecules to receptor sites on cellular plasma membranes. Insulin promotes uptakes of carbohydrates, proteins and fats in most tissues. It influences carbohydrate, protein and fat metabolism by stimulating protein and free fatty acid synthesis, and by inhibiting release of free fatty acid from adipose cells. Insulin increases active glucose transport through muscle and adipose cellular membranes, and promotes conversion of intracellular glucose and free fatty acid to the appropriate storage forms (glycogen and triglyceride, respectively).[22]

Even though the actions of exogenous insulin are identical to those of endogenous insulin, the ability to negatively affect hepatic glucose output differs on a unit per unit basis because a smaller quantity of an exogenous insulin dose reaches the portal vein. Administered insulin (human and analogues), substitutes for inadequate endogenous insulin secretion and partially corrects the disordered metabolism and inappropriate hyperglycaemia of diabetes mellitus, which are caused by either a deficiency or a reduction in the biologic effectiveness of endogenous insulin. Hypoglycaemia, hypokalemia, lipodystrophy and hysensitivity are among the potential clinical adverse effects associated with the use of all insulins.[22]

2.1. Insulin analogues

The newer insulin analogues have several improvements due to their modified action profile. It is claimed that the main advantages of rapid- acting preparations include the faster onset of action and shorter duration time of action. Long-acting analogues afford structural changes, which delay the onset of action, allow slow and continuous absorption into the systemic circulation and prolong the duration of action. Thus, producing a time-concentration profile, imitates the normal insulin basal level and leads to physiological basal glycaemic control with less nocturnal hypoglycaemia.[23]

2.1.1. Rapid-acting insulin analogues

a) Insulin Lispro
Insulin lispro (Humalog) is the first genetically engineered rapid-acting insulin analogue, approved for clinical use in 1996. Its structure differs from human insulin in the B-chain where proline at position 28 and lysine at position 29 are reversed, leading to a molecule with reduced capacity of self-association in solution (therefore faster absorbed, with higher peak serum levels and shorter action duration in comparison to regular human insulin). Besides glycaemic management, lispro improves the postprandial leptin and grehlin regulation of type 1 diabetic patients and may be used in cases of gestational diabetes.[23] Lispro insulin should be injected immediately prior to eating (or less than 15 minutes before the meal).[24]

b) Insulin Aspart
Insulin aspart (Novorapid) structure differs from human insulin at position 28 where proline is substituted with the charged aspartic acid, allowing it to be absorbed twice as fast as human insulin.[23] It should be given immediately before a meal (start of meal within five to ten minutes after injection).[24]

c) Insulin Glulisine
Insulin glulisine (Apidra) is the most recent rapid-acting analogue, launched in 2004. Its structure differs in two points from human insulin: asparagine at position 3 is substituted by lysine and lysine at position 29 by glutamic acid. These alterations reduce hexamers formation and enhance absorption from subcutaneous depots.[23] Insulin glulisine should be administered within 15 minutes before or within 20 minutes after starting a meal.[24]

2.1.2. Long-acting insulin analogues

a) Insulin Glargine
Insulin glargine (Lantus) is the first long-acting insulin analogue having amino-acid modifications in both chains. In the A-chain, the asparagine at position 21 is substituted by glycine and the B-chain is elongated at the C-terminus by addition of two arginine residues. Glargine is a molecule with a changed isoelectric point towards neutral, bearing decreased solubility at physiological pH. This causes precipitation after injection in the subcutaneous tissue, stabilisation of insulin hexamers, delay of their dissociation, and steady absorption into the circulation. Consequently, insulin glargine bears a stable serum concentration without pronounced peaks and significantly elongated duration of action, which covers the patient for 24 hours.[23] It was approved by United States Food and Drug Administration (U.S. FDA) in 2000.[25]

b) Insulin Detemir
Insulin detemir (Levemir) is characterised by acylation of myristic acid to the lysine residue at position 29 in the B-chain and deletion of the last threonine (position 30) in the B-chain. Its protracted action is achieved through delayed resorption caused by increased self-association reversible albumin binding at the injection site as well as because albumin binding causes buffering of insulin concentration. This results in a flat, prolonged pharmacodynamic profile, which provides a metabolic effect for approximately 17 hours.[23] It was approved by U.S. FDA in 2005.[25]

2.1.3. Premixed insulin analogues

a) Novolog® Mix 70/30
Novolog® Mix70/30 (70% insulin aspart suspension and 30% insulin aspart injection) is a human insulin analog suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. It has an earlier onset and intermediate duration of action in comparison with basal human insulin. The recommended interval between dosing and meal initiation is 10-20 minutes.[26]

b) Humalog® Mix 75/25

Novolog® Mix75/25 (75% insulin lispro suspension and 25% insulin lispro injection) is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood-glucose lowering agent. It should be administered immediately before a meal (within 15 minutes).[26]

c) Humalog® Mix 50/50

Novolog® Mix50/50 (50% insulin lispro suspension and 50% insulin lispro injection) is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood-glucose lowering agent.[15]

Table 1. Main characteristics of rapid-acting, long-acting and premixed insulin analogues.[24,26,27]

ANALOGUE	TRADE NAME / MANUFACTURER	ONSET	PEAK	DURATION
Rapid-acting analogues				
Lispro	Humalog/Eli Lilly	15-30 minutes	0.5 - 2.5 hours	2-4 hours (max:≤5 hours)
Aspart	Novolog/Novo Nordisk	12-18 minutes	1-3 hours	3-5 hours
Glulisine	Apidra/Sanofi-Aventis	12-30 minutes	1.6 – 2.8 hours	3-4 hours
Long-acting analogues				
Glargine	Lantus/Sanofi-Aventis	3-4 hours	No peak	22 to 24 hours
Detemir	Levemir/Novo Nordisk	3-4 hours	3-9 hours	Up to 24 hours (Mean duration of action of insulin detemir ranged from 5.7 hours at the lowest dose to 23.2 hours at the highest dose)
Premixed insulin analogues				
75% neutral protamine lispro, 25% lispro	75/25 Humalog/Eli Lilly	10-30 minutes	1.0-6.5 hours	14-24 hours
70% protamine aspart, 30% aspart	70/30 Novolog/Novo Nordisk	10-20 minutes	1-4 hours	18-24 hours

2.2. Human insulin

Human insulin is more recent than animal insulin. The first synthetic human insulin was approved by U.S. FDA for pharmaceutical use in 1982.

2.2.1. Short-acting insulin

a) Regular Human Insulin (Humulin®, Novolin®)

Novolin R is a sterile, aqueous, and colourless solution of human insulin with a short duration of action. The pharmacologic effect of Novolin R begins approximately one-half hour after subcutaneous administration. The effect is maximal between two-half hours and five hours and terminates after approximately eight hours. It is best if administered 30 minutes before meal.[22]

2.2.2. Intermediate-acting insulin

a) NPH Human Insulin (Novolin® N, Humulin® N)
- Humulin N [Human insulin (rDNA origin) isophane suspension] is a crystalline suspension of human insulin with protamine and zinc providing an intermediate-acting insulin with a slower onset of action (1 to 2 hours) and a longer duration of activity (up to 24 hours) than that of regular human insulin. Humulin N is a sterile suspension and for subcutaneous injection only.

- Novolin n InnoLet is a cloudy or milky suspension of human insulin with protamine and zinc. The effect of Novolin n begins approximately one-half hours after injection. The effect is maximal between four and 12 hours. The full duration of action may last up to 24 hours after injection.[28]

2.2.3. Premixed human insulin

a) Novolin 70/30® – Humulin 70/30®
- Mixture of 70% NP, Human Isophane Suspension and 30% Regular human insulin injection. The recommended interval between dosing and meal initiation is 30 minutes.[26]

3.   POLICY QUESTION

In Ministry of Health facilities, should insulin analogues be used for all diabetic patients treated with insulin?

4.   OBJECTIVE

4.1. To assess the safety and efficacy or effectiveness of rapid-acting, long-acting or premixed insulin analogues compared with conventional human insulin in treatment of type 1, type 2, or gestational diabetes mellitus.

4.2. To assess the economic implications of using insulin analogues in treatment of type 1, type 2, or gestational diabetes mellitus.

The following research questions were addressed:-
- How safe is rapid-acting, long-acting or premixed insulin analogues compared with conventional human insulin in treatment of type 1, type 2, or gestational diabetes mellitus?

- What are the short and long term benefits of using rapid-acting, long-acting or premixed insulin analogues compared with conventional human insulin in treatment of type 1, type 2, or gestational diabetes mellitus?

- What are the economic implications of using insulin analogues in the treatment of type 1, type 2, or gestational diabetes mellitus?

5.   METHODS

5.1.   Literature search strategy

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2012), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2012), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2012), EBM Reviews-Health Technology Assessment (1st Quarter 2012), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2012). Parallel searches were run in PubMed. No limits were applied to the search, except for publication year from 2006 to current for EBM Reviews-Cochrane Central Register of Controlled Trials. Appendix 3 showed the detailed search strategies. Other database searched include FDA database. The last search was run on 7 March 2012. Additional articles were identified from reviewing the references of retrieved articles and contacting the authors. General search engine was used to get additional web-based information.

5.2.   Study selection

Based on the policy question the following inclusion and exclusion criteria were used:-

5.2.1. Inclusion criteria

- Studydesign:
  - HTA report, Systematic Review, Randomised Controlled Trials (RCT) and studies which include economic evaluation.
- Population:
  - Patients with diabetes mellitus (type 1, type 2, or gestational).
- Intervention:
  - Rapid-acting insulin analogues: (insulin lispro or insulin aspart or insulin glulisine).
  - Long-acting insulin analogues (insulin glargine or insulin detemir).
  - Premixed insulin analogues (insulin 75% neutral protamine, 25% lispro or 50% neutral protamine, 50% lispro or 70% protamine aspart, 30% aspart).
- Comparators:
  - Regular human insulin.
  - Neutral Protamine Hagedorn (NPH insulin).
  - Premixed insulin preparations (NPH/ regular 70/30, NPH/regular 50/50).
  - Combination of conventional human insulin with oral anti-diabetic agents (OADs) or IA.
- Outcome:
  - Glycaemic control; glycosylated haemoglobin (HbA1c), fasting plasma glucose, 24 hour glucose profile, glucose variability.
  - Hypoglycaemic episodes (overall, severe, nocturnal hypoglycaemia episodes and neonatal hypoglycaemia).
  - Quality of life assessment.
  - Adverse events or complications related to the use of insulin analogues (for example local reaction, carcinogenicity, teratogenicity, and sudden intrauterine demise among gestational diabetes).
  - Diabetic complications (nephropathy, retinopathy, neuropathy, and other diabetes related complications).
  - Mortality (total and diabetes related mortality).
  - Weight changes.
  - Costs.
- Treatment duration: Four weeks and above.
- Full text articles published in English.

5.2.2. Exclusion criteria

- Study design: Animal study, laboratory, narrative review, cross-sectional study, cohort and case control studies.
- Non English full text article.
- Studies which compare insulin analogue with another insulin analogue.

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. The titles and abstracts of all studies were assessed for the above eligibility criteria. If it was absolutely clear from the title and/or abstract that the study was not relevant, it was excluded. If it was unclear from the title and/or abstract the full text article was retrieved. Two reviewers assessed the content of the full text articles. Disagreement was resolved by discussion.

5.3. Quality assessment strategy

The methodological quality of all the relevant full text articles retrieved was assessed using the Critical Appraisal Skills Programme (CASP) tool for systematic review (including HTA reports) and economic evaluation.[29] For RCT, quality was assessed using Jadad scale for reporting randomised controlled trials.[30] Quality assessment was conducted by two reviewers. All full text articles were graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1).[31]

5.4. Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 4) and checked by another reviewer. Disagreements were resolved by discussion. Details on: (1) methods including study design, (2) study population characteristics including gender, age, type of diabetes, duration of diabetes, (3) type of intervention [rapid-acting (short-acting), long-acting or premixed insulin analogues], (4) type of comparators (regular human insulin, NPH insulin, premixed human insulin) (5) type of outcome measures including: a) glycaemic control; glycosylated Haemoglobin (HbA1c), fasting plasma glucose, 24 hour glucose profile, glucose variability b) hypoglycaemic episodes (overall number, severe episodes, nocturnal hypoglycaemia episodes and neonatal hypoglycaemia), c) quality of life, d) adverse events or complications related to the use of insulin analogues such as local reaction, carcinogenicity, teratogenicity, and sudden intrauterine demise among gestational diabetes, e) diabetic complications (nephropathy, retinopathy, neuropathy, and other related complications), f) mortality, g) weight changes, h) economic evaluation and (6) treatment duration were extracted. The extracted data were presented and discussed with the expert committee.
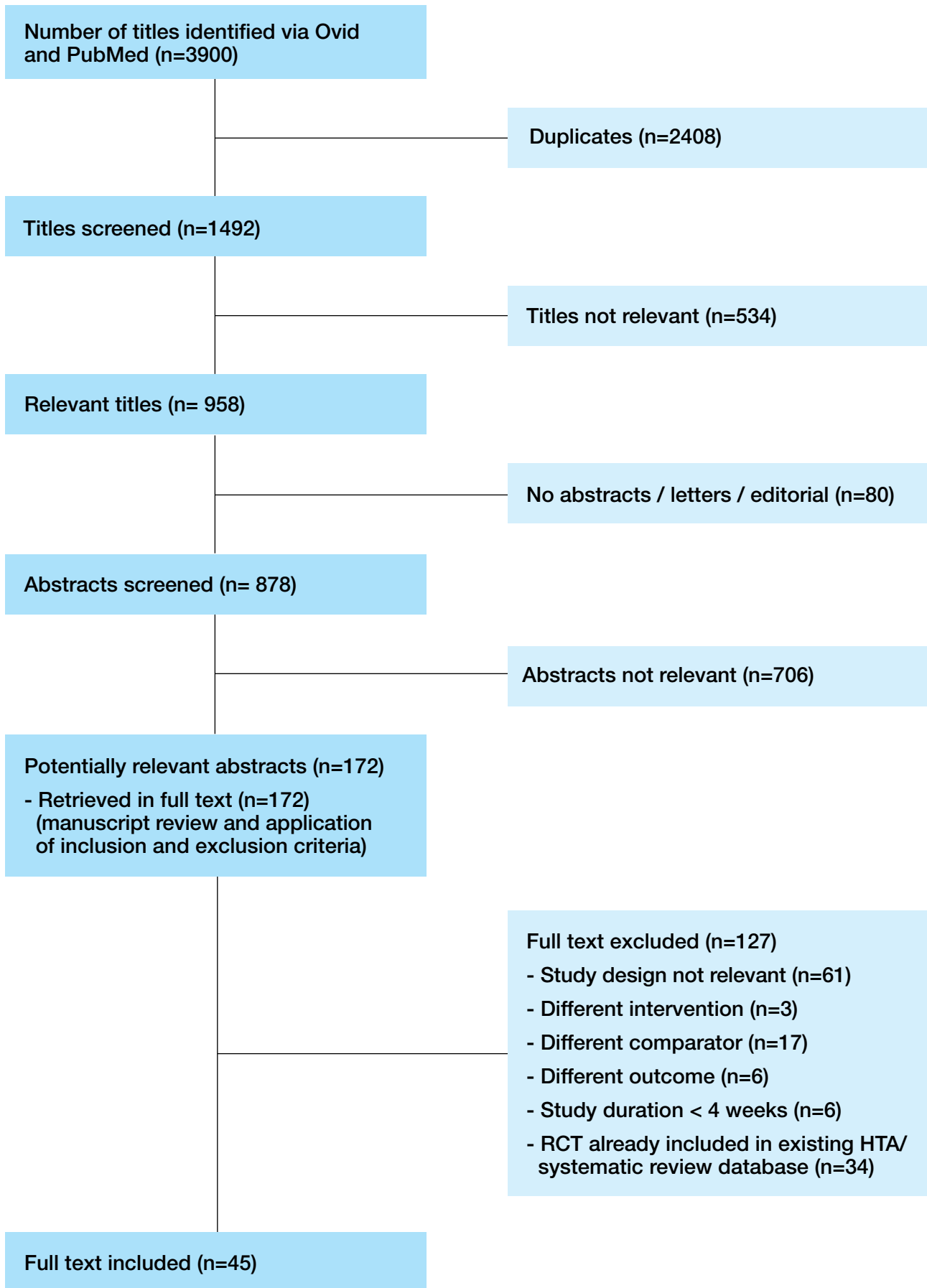
5.5. Methods of data synthesis

Data on the safety, efficacy and cost implication of using insulin analogues in the treatment of type 1, type 2, or gestational diabetes mellitus were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6. RESULTS

A total of 3,900 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2012), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2012), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2012), EBM Reviews-Health Technology Assessment (1st Quarter 2012), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2012) and PubMed. After removal of duplicates, 1,492 titles were screened and 958 were found to potentially relevant. A total of 878 abstracts were screened using the inclusion and exclusion criteria. Of these, 706 abstracts were found to be irrelevant. One hundred and seventy two potentially relevant abstracts were attempted for retrieval of full text. After reading, appraising and applying the inclusion and exclusion criteria to 172 full text articles, 45 full text articles were included as shown in Figure 1 and 127 full text articles were excluded.The excluded studies are listed in Appendix 5. The 45 full text articles finally selected for this review comprised of five HTA reports, 10 systematic reviews, 16 RCTs, 13 cost-effectiveness analyses and one costing analysis.

Figure 1. Flow chart of study selection

Number of titles identified via Ovid and PubMed (n=3900)

Duplicates (n=2408)

Titles screened (n=1492)

Titles not relevant (n=534)

Relevant titles (n= 958)

No abstracts / letters / editorial (n=80)

Abstracts screened (n= 878)

Abstracts not relevant (n=706)

Potentially relevant abstracts (n=172)

- Retrieved in full text (n=172)
  (manuscript review and application
  of inclusion and exclusion criteria)

Full text excluded (n=127)

- Study design not relevant (n=61)

- Different intervention (n=3)

- Different comparator (n=17)

- Different outcome (n=6)

- Study duration < 4 weeks (n=6)

- RCT already included in existing HTA/
  systematic review database (n=34)

Full text included (n=45)

6.1. Efficacy or effectiveness of insulin analogues

6.1.1. Rapid-acting insulin analogues

a) Insulin Lispro

In comparing insulin lispro (ILis) with human insulin, we included three level I studies [one HTA report (Barnajee *et al.*) and two systematic reviews (Singh *et al.*, Siebenhofer *et al.*)]. We also included one more recent RCT (Brunetti *et al.* 2010). The studies covered paediatric, adolescent and adult population.

i. Type 1 diabetes mellitus

Glycaemic control

In adults, compared with regular human insulin, use of insulin lispro resulted in a small but statistically significant reduction of HbA1c by 0.09% (Barnajee *et al.*, Singh *et al.*) and by 0.11% (Siebenhofer *et al.*) as shown in Table 2.[32-34 level I] In contrast, a more recent multicentre, randomised, parallel-group, open label, non-inferiority, Phase III trial conducted in Italy comparing insulin glargine plus insulin lispro with insulin glargine plus regular human insulin (RHI) reported no significant difference in HbA1c level at the end of the 28 weeks study period.[35 level I] Barnajee *et al.* also reported that in many trials, insulin lispro significantly lowered blood glucose profiles after meals: postbreakfast (19 trials), postlunch (12 trials) and postdinner (15 trials). The weighted mean difference (WMD) and 95% confidence interval (CI) values for two-hour postprandial blood glucose was -1.25 mmol/L (-1.70 to -0.79 mmol/L).[32 level I] Similar trend was reported by Brunetti *et al.* [35 level II-I] There was no statistically significant difference between the two groups for fasting and preprandial blood glucose levels.[32 level I,35 level II-I]

In children, the pooled analysis of trials comparing insulin lispro with human insulin found no statistically significant difference in HbA1c.[32-33 level I] Similarly, no statistically significant difference in HbA1c was observed for prepubertal and adolescents.[32-33 level I]

Quality of life (QoL)

Barnajee *et al.* reported that overall, type 1 patients prefer insulin lispro compared to human insulin because of its convenience when using as it can be used immediately before meal. In terms of well being, there was limited evidence showing that insulin lispro is better than human insulin.[32 level I] In another systematic review, out of seven studies that used the Diabetes Treatment Satisfaction Questionnaire (DTSQ), three studies found no significant difference between treatment arms while four observed improvement in the analogue arm.[34 level I] Using the Well-being Enquiry for Diabetics (WED) questionnaire, Brunetti *et al.* demonstrated similar QoL between insulin lispro group and human regular insulin group: mean WED score=2.09 ± 0.50 in the RHI group versus 2.09 ± 0.49 for the lispro group.[35 level II-I]

Table 2. Summary of glycaemic efficacy / effectiveness for insulin lispro in type1 and type 2 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Barnajee (2007)	Systematic review and meta-analysis (Database until Jan. 2006)	Type 1	ILis (or ILismix) versus RHI (or HIMix)	• HbA1c (all patients, 34 trials, 8,435) [WMD (95% CI) = -0.09% (-0.16 to -0.01%)] Adult patients (29 trials, 7,102) [WMD (95% CI) = -0.10% (-0.18 to -0.02%)] Paediatric patients (5 trials, 1,333) [WMD (95% CI) = -0.01% (-0.26 to 0.24%)] • Eight-point blood glucose profiles Lower blood glucose profiles after meals (post-breakfast, postlunch and postdinner) compared with HI. • Fasting blood glucose (233 patients) [WMD (95% CI) = -0.74 mmol/L (-1.62 to 0.13)] • Preprandial (2,014 patients) [WMD (95% CI) = 0.27 mmol/L (-0.10 to 0.65)] • 2-hour postprandial (2,210 patients) [WMD (95% CI) = -1.25 mmol/L (-1.70 to -0.79)]
		Type 2		• HbA1c (all patients, 10 trials, 2,844) [WMD (95% CI) = -0.11% (-0.22 to 0.00%)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 1	ILis versus RHI	• HbA1c (22 trials, 6,021 patients) [WMD (95% CI) = -0.09% (-0.16 to -0.02%)] Children (4 trials, 286 patients) [WMD (95% CI) = 0.14% (-0.18 to 0.46%)] Adolescents (1 trial, 926 patients) [WMD (95% CI) = -0.01% (-0.21 to 0.19%)]
		Type 2		• HbA1c (11 trials, 3,093 patients) [WMD (95% CI) = -0.03% (-0.12 to 0.06%)]
Siebenhofer (2006, edited 2009)	Systematic review and meta-analysis (Database until 2005)	Type 1 (adult)	ILis versus RHI	• HbA1c (15 studies) [WMD (95% CI) = -0.11% (-0.18 to -0.04%)] Prepubertal and adolescents with type 1 diabetes mellitus – no significant reduction in HbA1c
Brunetti (2010)	Multicentre, parallel-group, open label RCT (study period=28 weeks)	Type 1	Insulin glargine and insulin lispro versus insulin glargine and RHI	At the end of study:- • HbA1c (Mean ± SD) - RHI group (7.10 % ± 0.83%) - Insulin lispro group (6.95 % ± 0.78%), p>0.05 • Fasting Plasma glucose (Mean ± SD) - RHI group (164.6 mg/dL ± 42.4 mg/dL) - Insulin lispro group (169.2 mg/dL ± 41.8 mg/dL), p=0.2458 • Trend of lower post-prandial blood glucose levels in lispro compared to RHI group

Footnote:

WMD: Weighted Mean Difference

ii. Type 2 diabetes mellitus

Glycaemic control

For type 2 diabetes mellitus, a HTA report and a systematic review reported no statistical significant differences between insulin lispro and regular human insulin treatments.[32-33 level I] In the HTA report by Barnajee *et al.* the WMD (95% CI) for HbA1c from 10 trials involving 2,844 patients was -0.11% (-0.22 to 0.00%).[32 level I] Similarly, Singh *et al.* reported that the WMD (95% CI) for HbA1c from a pooled analysis of 11 trials involving 3,093 patients was -0.03% (-0.12 to 0.06%).[33 level I] Barnajee *et al.* reported that patients with type 2 diabetes treated with insulin lispro had a better control of postprandial blood glucose compared with human insulin or oral antidiabetics (OADs).[32 level I]

Quality of life (QoL)

Barnajee *et al.* reported that for type 2 diabetes mellitus patients, two trials did not show any differences in terms of treatment satisfaction or patients well being.[32 level I]

iii. Gestational diabetes mellitus and pregnant women with type 1 diabetes

Glycaemic control

In pooled analysis of results from studies comparing insulin lispro with regular human insulin in pregnant women with type 1 diabetes, Singh *et al.* found no statistically significant differences in HbA1c [WMD (95% CI) = 0.20% (-1.03 to 1.43%)].[33 level 1] Similarly, Siebenhofer *et al.* found similar reduction in HbA1c in patients treated with insulin lispro and human insulin.[34 level 1] There was also no statistically significant difference in HbA1c among women with gestational diabetes treated with insulin lispro compared with human insulin.[32-34 level I] The HbA1c WMD and 95% CI was 0.06% (-0.11 to 0.23%).[32-33 level I]

b. Insulin aspart

In comparing insulin aspart (IAsp) with human insulin, we included four level I studies [one HTA report (Barnajee *et al.*) and three systematic reviews (Singh *et al.*, Siebenhofer *et al.*, Rys *et al.*)]. We also included two RCTs (Mathiesen *et al.*, Pettitt *et al*.) for gestational diabetes mellitus (GDM) and pregnant women with type 1 diabetes. The summary of glycaemic efficacy / effectiveness for insulin aspart in type 1 and type 2 diabetes mellitus patients are shown in Table 3.

Table 3. Summary of glycaemic efficacy / effectiveness for insulin aspart in type 1 and type 2 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Barnajee (2007)	Systematic review and meta-analysis (Database until Jan. 2006)	Type 1	IAsp (or IAspMix) versus HI (or HIMix)	• HbA1c (all patients, 8 trials, 2,948) [WMD (95% CI) = -0.14% (-0.22 to -0.07%)] • Eight-point blood glucose profiles Lower blood glucose profiles after meals (postbreakfast, postlunch and postdinner) compared with HI.
		Type 2		• HbA1c (all patients, 6 trials, 750) [WMD (95% CI) = -0.09% (-0.23 to 0.05%)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 1	IAsp versus RHI	• HbA1c (7 trials, 3,095 patients) [WMD (95% CI) = -0.13% (-0.20 to -0.07%)]
		Type 2		• HbA1c (6 trials, 1,031 patients) [WMD (95% CI) = -0.09% (-0.12 to 0.04%)]
Siebenhofer (2006, edited 2009)	Systematic review and meta-analysis (Database until 2005)	Type 1 (adult)	IAsp versus RHI	• HbA1c (6 studies) [WMD (95% CI) = -0.11% (-0.19 to -0.03%)] • Prepubertal and adolescents with type 1 diabetes mellitus – no significant reduction in HbA1c
Rys P (2011)	Systematic review and meta-analysis (Database until July 2009)	Type 1	IAsp (or BIAsp) versus RHI (or biphasic human insulin)	• HbA1c (all patients, 13 studies) [WMD (95% CI) = -0.11% (-0.16 to -0.06%)] • Fasting blood glucose (5 studies, 2,138 patients) [WMD (95% CI) = 0.15 mmol/L (-0.55 to 0.86)] • Postbreakfast glucose (5 studies, 2,820 patients) [WMD (95% CI) = -1.43 mmol/L (-1.75 to -1.11)] • Postlunch glucose (5 studies, 2,712 patients) [WMD (95% CI) = -1.11 mmol/L (-1.61 to -0.61)] • Postdinner glucose (6 studies, 3,138 patients) [WMD (95% CI) = -0.97 mmol/L (-1.25 to -0.69)]
		Type 2		• HbA1c (all patients, 9 studies) [WMD (95% CI) = -0.04% (-0.10 to 0.03%)] • Postbreakfast glucose (3 studies, 512 patients) [WMD (95% CI) = -0.83 mmol/L (-1.45 to -0.21)] • Postlunch glucose (2 studies, 225 patients) [WMD (95% CI) = -1.32 mmol/L (-2.16 to -0.49)]

Footnote:

WMD: Weighted Mean Difference

i. Type 1 diabetes mellitus

Glycaemic control

Four systematic reviews and meta-analysis comparing the use of insulin aspart with human insulin demonstrated that the use of insulin aspart resulted in a small but significant reduction of HbA1c ranging from 0.11% to 0.14% as shown in Table 3.[32-34 level I,36 level I] Barnajee *et al.* also reported that the use of insulin aspart was associated with a lower blood glucose profiles after meals (postbreakfast, postlunch and postdinner) compared with human insulin.[32 level I] Similarly, in more recent systematic review by Rys *et al.* the pooled analysis of postprandial glucose significantly favoured insulin aspart. The WMD (95% CI) for postbreakfast glucose was -1.43 mmol/L (-1.75 to -1.11 mmol/L), postlunch glucose was -1.11 mmol/L (-1.61 to -0.61 mmol/L) and postdinner glucose was -0.97 mmol/L (-1.25 to -0.69 mmol/L).[36 level I]

Quality of life (QoL)

Rys *et al.* reported that the DTSQ was used to assess treatment satisfaction in three studies, but on treatment flexibility was assessed in only two of them. Patients in the insulin aspart group scored significantly better for total DTSQ: Standardized mean difference (SMD) and 95% CI was 0.30 (0.20 to 0.40) as well as for DTSQ treatment flexibility [WMD (95% CI) = 0.31 (0.15 to 0.47)].

Also, statistically significant superiority of insulin aspart was found using the Diabetes-Specific Quality-of-Life Scale (DSQOLS) concerning dietary restrictions in one study whereby significant improvement in QoL was reported in 23% of insulin aspart group and 14% of the regular human insulin group. The other study reported no significant difference in QoL based on Diabetes Health Profile (DHP) questionnaire.[36 level I]

ii. Type 2 diabetes mellitus

Glycaemic control

Treatment with insulin aspart did not result in a significant reduction in HbA1c level compared with human insulin in type 2 diabetes as demonstrated by pooled analysis of studies in these systematic reviews.[32-33, 36 level 1] However, treatment with insulin aspart was found to reduce the postprandial blood glucose. The pooled analysis revealed a difference favouring insulin aspart. The WMD (95% CI) for postbreakfast glucose was -0.83 mmol/L (-1.45 to -0.21) and postlunch glucose was -1.32 mmol/L (-2.16 to -0.49).[36 level I]

iii. Gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus

Glycaemic control

The efficacy and safety of insulin aspart in pregnant women with type 1 diabetes mellitus was evaluated by Mathiesen *et al.* among 322 patients. A total of 157 patients were treated with insulin aspart while 165 patients were treated with regular human insulin. They found that HbA1c was comparable with human insulin in the second and third trimesters. The [mean difference (MD)] and 95% CI for insulin aspart minus regular human insulin was -0.04% (-0.18 to 0.11%) for the second trimester and -0.08% (-0.23 to 0.06%) in the third trimester. A total of 80% of subjects achieved an HbA1c ≤ 6.5%. At the end of the first and third trimesters, average postprandial glucose increments were significantly lower with insulin aspart than human insulin (p=0.003 and p=0.001, respectively). [37 level II-I]

Pettitt *et al.* conducted a study to assess the efficacy and safety of insulin aspart for patients with gestational diabetes mellitus in 27 women whereby 14 were treated with insulin aspart and 13 were treated with regular human insulin. They found that both treatment groups maintained good overall glycaemic control during the study (beginning and end of study, HbA1c ≤ 6%).However, change from baseline values for average glucose were significantly lower for insulin aspart treatment than regular human insulin treatment: [Mean ± Standard Deviation (SD)] for insulin aspart was -1.09 ± 0.54 mmol/L and for regular human insulin was -0.54 ± 0.74 mmol/L, p = 0.003.[38 level II-I]

Quality of life (QoL)

Mathiesen *et al.* described that at follow-up, the isulin aspart group reported a significantly greater overall treatment satisfaction (87.6 ± 12.0) than the human insulin group (83.4 ± 15.3), p = 0.031.Between treatment differences were largely due to more insulin aspart treated patients reporting satisfaction with flexible treatment (DTSQ scores), [(IAsp = 85.9 ± 15.0 versus RHI = 75.8 ± 23.8)] and willingness to continue on present treatment [(IAsp = 90.1 ± 16.2 versus RHI = 81.9 ± 25.2)].[37 level II-I]

c. Insulin glulisine

This review identified one HTA report (Barnajee *et al.*) which reported findings comparing insulin glulisine with regular human insulin. For type 1 diabetes mellitus, one RCT with 564 patients showed no significance difference in HbA1c levels. From the pooled analysis of two studies involving 1,768 type 2 diabetes patients, there was also no statistically significant difference in HbA1c levels. The WMD (95% CI) was -0.03% (-0.18 to 0.11%).[32 level I]

d. Rapid-acting insulin analogues (Insulin lispro, insulin aspart)

Two systematic reviews described the findings of insulin lispro together with insulin aspart when compared with regular human insulin. Plank *et al.* conducted a systematic review and meta-analysis on rapid-acting insulin analogues compared with regular human insulin. The Cochrane Library, MEDLINE and EMBASE were searched until 2003. A total of 42 RCTs with 7,933 patients were included in the review. Pooled analysis from 20 studies for adult patients with type 1 diabetes mellitus found that the WMD (95% CI) between HbA1c values obtained using rapid-acting insulin analogues and regular human insulin was -0.12% (-0.17 to -0.07%) favouring rapid-acting insulin analogues. For patients with type 2 diabetes mellitus, the WMD (95% CI) between HbA1c values obtained using rapid-acting insulin analogues and regular human insulin was -0.02% (-0.10 to -0.07%). No differences between treatments were observed in children with type 1diabetes mellitus, pregnant women with type 1 diabetes mellitus, and women with gestational diabetes mellitus.[39 level I] Similar findings were reported by Siebenhofer *et al.* in 2009. The WMD (95% CI) between HbA1c values obtained using rapid-acting insulin analogues and regular human insulin was -0.10% (-0.16 to -0.05%) for adult patients with type 1 diabetes mellitus and -0.03% (-0.11 to 0.04%) for patients with type 2 diabetes mellitus.[34 level I]

6.1.2. Long-acting insulin analogues

a) Insulin glargine

In evaluating the efficacy or effectiveness of insulin glargine (IGlar) compared with human insulin, we included six level I studies [3 HTA reports (Tran *et al.*, Waugh *et al.*, Warren *et al.*) and 3 systematic reviews with meta-analysis (Singh *et al.*, Horvath *et al.*, Bazzano *et al.*)].We also included five RCTs (Bolli *et al.*, Chase *et al.*, Wu *et al.*, Aswell *et al.*, and Mattia *et al.*).

i. Type 1 diabetes mellitus

Glycaemic control

In adults, compared with NPH insulin, the use of insulin glargine resulted in a small but statistically significant reduction of HbA1c by 0.11% (Singh *et al.*).[33 level I] In the HTA report by Tran *et al.* data for HbA1c from 11 trials were not pooled because of high heterogeneity (I^2 >75%). However, they found the HbA1c levels were lowered to a greater degree in insulin glargine compared to NPH group in some trials.[40 level I] Warren *et al.* in 2004 also reported similar findings as shown in Table 4.[41 level I] Bolli *et al.* conducted a multicentre, parallel group, open-label RCT among 175 adults. They found that baseline to endpoint change in HbA1c was similar in both treatment groups (-0.56% in insulin glargine versus -0.56% in NPH). However, they found that the improvement of fasting blood glucose (FBG) was significantly greater with insulin glargine than NPH [mean difference (95% CI):-18.2 mg/dL (-31.3 to -5.2 mg/dL, p = 0.0064)]. In terms of glucose variability, the study found that the mean daily blood glucose (MDBG) and mean amplitude of glycaemic excursion (MAGE) decreased significantly with insulin glargine but not with NPH. In the glargine group, MDBG (in patients with at least 7 glycaemic points / day) was significantly reduced at endpoint compared with baseline by (-10.1 mg/dL; 95% CI:-18.1 to -2.1 mg/dL, p = 0.0126). The once daily glargine group demonstrated a statistically significant difference from baseline to endpoint in MAGE by (-20.2 mg/dL; 95% CI:-34.5 to -5.9 mg/dL, p = 0.0056).[42 level II-I]

Table 4 showed that in children and adolescents, pooled analysis of trials comparing insulin glargine with NPH insulin found no statistically significant difference.[33 level I] Chase *et al.* conducted a randomised, open-label gender-stratified, 2-arm, parallel-group comparison of once-daily insulin glargine with twice-daily NPH/Lente in 175 adolescents (age between nine to 17 years). They found that the overall mean change in HbA1c from baseline to week 24 was similar in the two groups.[43 level II-I]

Table 4. Summary of glycaemic efficacy / effectiveness for insulin glargine in type 1 diabetes mellitus

STUDY	STUDY DESIGN	INTERVENTION	OUTCOME
Tran (2007)	Systematic review and meta-analysis (Database until Feb. 2006)	IGlar versus NPH	• HbA1c All patients (11 trials, 3,279), WMD not pooled, I^2=78.5% HbA1c levels were lowered to a greater degree in IGlar group compared to NPH group. • Fasting plasma glucose (6 trials, 1,682 patients) [WMD (95% CI) = -0.92 mmol/L (-1.21 to -0.63 mmol/L)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	IGlar versus NPH	• HbA1c (11 trials, 2,728 patients) [WMD (95% CI) = -0.11% (-0.21 to -0.02%)] • HbA1c Children and adolescents (4 trials, 680 patients) [WMD (95% CI) = -0.25% (-0.55 to 0.05%)]
Warren (2004)	Systematic review (Database until 2002)	IGlar versus NPH	• Summary of evidence Insulin glargine appears to be more effective than NPH in reducing fasting blood glucose (FBG) but not in reducing HbA1c and there is some evidence that both insulins were as effective as each other in both FBG and HbA1c control.
Bolli (2009)	Multicentre, parallel-group, open label RCT (study period =30 weeks)	IGlar versus NPH	Baseline to endpoint change:- • HbA1c (Mean) Similar (-0.56% in IGlar versus -0.56% in NPH) • Fasting Plasma glucose (Mean ± 95% CI) - Iglar -28.0 mg/dL (-37.3 to -18.7 mg/dL) - NPH -9.8 mg/dL (-19.1 to -9.5 mg/dL) - Mean difference between IGlar and NPH= -18.2 mg/dL (-31.3 to -5.2 mg/dL), p<0.0064
Chase (2008)	Parallel-group, open label RCT among adolescents (study period = 24 weeks)	IGlar versus NPH/Lente	Baseline to endpoint change:- • HbA1c (Overall mean change ± SD) - Iglar -0.25 % ± 0.14% - NPH -0.05 % ± 0.13% - Mean difference between IGlar and NPH/Lente, p=0.1725 However, an analysis of covariance, adjusting for baseline HbA1c, revealed a strong study arm effect on the slopes of the regression lines, indicating that the reduction in HbA1c was significantly greater with insulin glargine in those patients with higher baseline HbA1c values.

Footnote:
WMD: Weighted Mean Difference

Quality of life (QoL)

Tran *et al.* in their review included two RCTs that reported QoL data. One RCT reported patients being treated with insulin glargine showed no statistically significant difference in fear of hypoglycaemia compared with NPH patients (mean ± SD): 1.8 ± 0.13 versus 1.7 ± 0.13, p = 0.44. Whereas, one RCT reported that the scores on all items (satisfaction, convenience, flexibility, and willingness to continue) in the DTSQ were statistically significantly better with insulin glargine than with NPH. In the Well-Being Questionnaire (WBQ), there was no statistically significant difference between the two treatments in 80% of the items (depression, anxiety, energy, and positive well-being).[40] level I

The QoL was evaluated by Bolli *et al.* using the WED questionnaire. Data from 113 patients were evaluated for impact, 113 for the level of satisfaction, 108 for general worries, and 111 for diabetes-related worries. They found no statistically significant differences from baseline in any of the domains in either group at three and six months. Overall, changes in scores for each domain were similar in the two groups, except for diabetes-related worries, which showed greater improvements in the glargine group (p = 0.050).[42] level II-I

Ashwell *et al.* conducted a study to compare the QoL and treatment satisfaction using insulin glargine plus insulin lispro with that using NPH insulin plus unmodified human insulin in adults with type 1 diabetes managed with multiple injection regimens among 56 type 1 diabetes mellitus patients. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Audit of Diabetes Dependent Quality of Life Questionnaire (ADDQoL) were completed at baseline and at 16 weeks and 32 weeks, with additional interim DTSQ measurements. They reported that the present QoL improved with glargine plus lispro but did not change with NPH plus human insulin [end point scores; 1.6 ± 0.1 (mean ± SEM) versus1.3± 0.1: difference 0.3 (95% CI; 0.1 to 0.6, p = 0.014)]. The average weighted impact score (AWI) at baseline was −1.8 ± 1.2, (Mean ± SD) indicating an overall negative impact of diabetes on QoL. AWI score improved significantly with glargine plus lispro but changed little with NPH plus human insulin [-1.4 ± 0.1 (mean ± SEM) versus -1.7 ± 0.1: difference 0.3 (95% CI; 0.0 to 0.6, p = 0.033)]. Treatment satisfaction (DTSQ 36-0 scale score) at end point was markedly greater with glargine plus lispro compared with that of NPH plus human insulin [32.2 ± 3.4 versus 23.9 ± 7.2: mean difference 8.6 (95% CI; 6.5 to 10.6, p < 0.001)]. Significant differences favouring glargine plus lispro were found for five of six items of the treatment satisfaction scale: current satisfaction with treatment (5.4 ± 0.2 versus 3.8 ± 0.2, p < 0.001), convenience of treatment (5.3 ± 0.1 versus 4.1 ± 0.1, p < 0.001), flexibility of treatment (5.2 ± 0.1 versus 3.7 ± 0.2, p < 0.001), recommend to others (5.5 ± 0.2 versus 3.9 ± 0.2, p < 0.001 and satisfaction to continue current treatment (5.7 ± 0.2 versus 3.2 ± 0.2, p < 0.001).[44] level II-I

Body weight

Chase *et al.* reported that the body mass index (BMI) of adolescents with type 1diabetes mellitus did not increase significantly from baseline to week 24 in either treatment group (p = 0.257 in the insulin glargine group) and (p = 0.1568) in the NPH group. The BMI at week 24 was 23.0 kg/m2 for insulin glargine while for the NPH/Lente was 23.1 kg/m2.[43] level II-I

ii. Type 2 diabetes mellitus

Glycaemic control

Pooled analysis of studies comparing the HbA1c values in type 2 diabetes mellitus patients treated with insulin glargine versus NPH insulin did not find a statistically significant difference in the HbA1c values between the two treatment groups as shown in Table 5.[33,40,45-47 level I] Similarly, Warren *et al.* showed that there was no evidence that insulin glargine was more effective than NPH insulin in reducing either FBG or HbA1c and some evidence that both insulins were as effective as each other in both FBG and HbA1c control.[41 level I] There were also no statistically significant difference in the eight-point blood glucose and FPG between the two treatment groups.[40,47 level I]

Mu *et al.* conducted open-label RCT among 260 patients with type 2 diabetes mellitus to investigate the glycaemic variability between insulin glargine and NPH insulin. After three months of intervention, they found that the fasting plasma glucose was still similar between the two groups, but the HbA1c, 2-hour postprandial glucose were significantly lower in insulin glargine group than in NPH insulin group, $p < 0.05$. The coefficient of variation (CV)-FBG (Mean ± SD) was also significantly lower in the insulin glargine than in the NPH group: insulin glargine group (10.2% ± 4.2%) versus NPH insulin group (19.6 % ± 6.1%), mean difference between insulin glargine and NPH insulin, $p < 0.05$.[48 level II-I]

In contrast, in a randomised, open-label, two-way cross-over study among 20 type 2 diabetes mellitus patients treated with insulin glargine versus NPH insulin, Mattia *et al.* reported no statistically significant difference in the mean MAGE index and MDBG between insulin glargine and NPH insulin ($p = 0.603$ and $p = 0.701$ respectively). They found both insulins provided similar improvements in glycaemic control. However, postprandial blood glucose was significantly lower after a standard meal test performed at 13:00 h the day after insulin injection with insulin glargine versus NPH insulin ($p = 0.02$).[49 level II-I]

Quality of Life (QoL)

Horvath *et al.* identified one trial which reported results on treatment satisfaction with DTSQ. The trial reported a statistically significant more pronounced improvement of mean scores of treatment satisfaction for treatment with insulin glargine versus NPH insulin.[45 level I]

Table 5. Summary of glycaemic efficacy / effectiveness for insulin glargine in type 2 diabetes mellitus

STUDY	STUDY DESIGN	INTERVENTION	OUTCOME
Tran (2007)	Systematic review and meta-analysis (Database until Feb. 2006)	IGlar versus NPH	• HbA1c (all patients, 2,967) [WMD (95% CI) = 0.05% (-0.07 to 0.16%)] • Eight-point blood glucose No statistically significant difference between treatments • Fasting plasma glucose No statistically significant difference between treatments
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	IGlar with OADs versus NPH with OADs	• HbA1c (11 trials, 3,397 patients) [WMD (95% CI) = -0.05% (-0.13 to 0.04%)]
Horvath (2007, edited 2009)	Systematic review and meta-analysis	IGlar versus NPH	• HbA1c (4 studies, 1,568 patients) [WMD (95% CI) = 0.05% (-0.08 to 0.17%)]
Waugh (2010)	Systematic review and meta-analysis (Database until April 2008)	IGlar versus NPH	• HbA1c (10 trials, 3,915 patients) [WMD (95% CI) = 0.00% (-0.11 to 0.10%)]
Bazzano (2008)	Systematic review and meta-analysis (Database until March 2007)	IGlar versus NPH	• HbA1c (12 trials) [Mean Net Change (95% CI) = 0.08% (-0.04 to 0.21%)] • Fasting plasma glucose 11 trials) [Mean Net Change (95% CI) = 0.21 mmol/L (-0.02 to 0.45 mmol/L)]
Warren (2004)	Systematic review (Database until 2002)	IGlar versus NPH	• Summary of evidence There is no evidence that insulin glargine is more effective than NPH in reducing either FBG or HbA1c and some evidence that both insulins are as effective as each other in both FBG and HbA1c control.

Mu (2011)	Open label RCT (study period = 3 months)	IGlar versus NPH	At the end of the study:-
			• HbA1c (Mean ± SD)
			  - IGlar (6.52% ± 1.34%)
			  - NPH (7.63% ± 1.18%),
			  - Mean difference between IGlar and NPH, p<0.05
			
			• Fasting Plasma glucose (Mean ± SD) Similar (5.50 mmol/L in IGlar versus 5.42 mmol/L in NPH)
			
			• 2-hour postprandial (Mean ± SD)
			  - IGlar (7.71 mmol/L ± 0.52 mmol/L)
			  - NPH (8.26 mmol/L ± 0.63),
			  - Mean difference between IGlar and NPH, p<0.05

Mattia (2009)	Randomised, open-label, single centre, two way cross-over study (study period = 27 weeks)	IGlar plus OADs versus NPH plus OADs	Baseline to endpoint change:- • HbA1c (Mean ± SD) Similar change (-1.7% in IGlar versus -1.6% in NPH) • Meal test Postprandial blood glucose was significantly lower after a standard meal test performed at 13:00 h the day after insulin injection with insulin glargine versus NPH (P=0.02).

Footnote:

WMD: Weighted Mean Difference

Body weight

The systematic review by Waugh *et al.* reported that the glargine groups (8 studies) gained 0.23 kilogram (kg) less weight than the NPH groups (range -1.10 to +0.23 kg). However, meta-analysis could not be performed due to too many missing standard deviations.[46 level I] The effect of treatment with insulin glargine compared with NPH insulin for body weight was evaluated by Bazzano *et al.* The pooled mean net change in body weight from the six trials was -0.33 kg (95% CI: -0.61 to -0.06 kg) favouring NPH. [47 level I]

iii. Gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus

This review did not retrieve any HTA report, systematic review or RCT reporting on the efficacy/ effectiveness of treatment with insulin glargine compared with NPH insulin in gestational diabetes mellitus patients and pregnant women with type 1 diabetes mellitus.

b) Insulin detemir

Two HTA reports, three systematic reviews and three RCTs were included in comparing the efficacy or effectiveness of insulin detemir with human insulin. The HTA reports were by Tran *et al.* and Waugh *et al.*, while the systematic reviews included were by Singh *et al.*, Horvath *et al.*, and Szypowska *et al.* Two more recent RCTs included for type 1 diabetes mellitus patients were by Thalange *et al.* and Zachariah *et al.*, while for type 2 diabetes mellitus patients the RCT by Fajardo *et al.* was also included in this review. The summary of glycaemic efficacy / effectiveness for insulin detemir in type 1 and type 2 diabetes mellitus compared with NPH insulin is shown in Table 6.

i. Type 1 diabetes mellitus

Glycaemic control

For adults with type 1 diabetes mellitus, one HTA report (Tran *et al.*), one systematic review (Singh *et al.*), and one RCT (Zachariah *et al.*) did not find any significant difference in the HbA1c values in patients treated with insulin detemir compared with NPH insulin.[33,40 level I,50 level II-I] In contrast, a more recent systematic review and meta-analysis by Szypowska *et al.* (2011) reported a small but statistically significant reduction in HbA1c, [WMD (95% CI):-0.073% (-0.0135 to -0.011%)] and for fasting plasma glucose,[WMD (95% CI): -0.977 mmol/L (-1.395 to -0.558 mmol/L)].[51 level I] Furthermore, pooled analysis of six trials by Tran *et al.* also showed a statistically significant reduction in fasting plasma glucose in patients treated with insulin detemir compared with NPH insulin, [WMD (95% CI): -0.87 mmol/L (-1.27 to -0.46 mmol/L)].[40 level I]

In children and adolescents, one trial showed no significant difference in HbA1c.[33 level I]. In a 52 week multinational, multicentre, open-label, randomised, two-armed parallel-group trial, Thalange *et al.* compared the efficacy and safety of insulin detemir with NPH insulin in 82 children (aged two to five years old) from 10 European countries. Mean HbA1c was similar between groups at baseline and after one year. However, the decreased in mean fasting plasma glucose was greater in those who received insulin detemir compared with NPH insulin (-1.0 mmol/L in insulin detemir versus -0.45 mmol/L in NPH insulin).[52 level II-I]

Table 6. Summary of glycaemic efficacy / effectiveness for insulin detemir in type 1 and type 2 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Tran (2007)	Systematic review and meta-analysis (Database until Feb. 2006)	Type 1 Type 2	IDet versus NPH	• HbA1c (8 trials, 2,937 patients) [WMD (95% CI) = -0.05% (-0.12 to 0.03%)] • Fasting plasma glucose (6 trials, 2,362 patients) [WMD (95% CI) = -0.87 mmol/L (-1.27 to -0.46 mmol/L)] • HbA1c (8 trials, 2,937 patients) [WMD (95% CI) = 0.11% (-0.03 to 0.26%)] • Eight-point blood glucose and fasting plasma glucose No significant difference
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 1 Type 2	IDet versus NPH IDet versus NPH with OADs versus NPH with OADs	• HbA1c (7 trials, 2,558 patients) [WMD (95% CI) = -0.06% (-0.13 to 0.02%)] • HbA1c (1 trial, 347 patients) [WMD (95% CI) = 0.10% (-0.01 to 0.30%)] • HbA1c (3 trials, 1,159 patients) [WMD (95% CI) = 0.13% (0.03 to 0.22%)]
Horvath (2007, edited 2009)	Systematic review and meta-analysis	Type 2	IGlar versus NPH	• HbA1c (2 studies, 967 patients) [WMD (95% CI) = 0.12% (0.01 to 0.23%)]
Waugh (2010)	Systematic review and meta-analysis (Database until April 2008)	Type 2	IGlar versus NPH	• HbA1c (4 trials, 1,584 patients) [WMD (95% CI) = 0.07% (-0.03 to 0.18%)]
Szypowska (2011)	Systematic review and meta-analysis (Database until Nov. 2010)	Type 1	IGlar versus NPH	• HbA1c (10 trials, 3,758 patients) [WMD (95% CI) = -0.073% (-0.0135 to -0.011%)] • Fasting plasma glucose (10 trials, 3,748 patients) [WMD (95% CI) = -0.977 mmol/L (-1.395 to -0.558 mmol/L)]

Thalange (2011)	Open-label, parallel group RCT (study period=52 weeks)	Type 1
		
		Children between 2 to 5 years
			IGlar versus NPH	At one year:
				• Mean HbA1c
				  - IDet (8.2 % at baseline versus 8.1% at 1 year)
				  - NPH (8.1 % at baseline versus 8.3% at 1 year)
				• Mean fasting plasma glucose
				  - Decreased by -1.0 mmol/L in IDet versus -0.45 mmol/L in NPH

Fajardo (2008)	Open-label, parallel group RCT (study period=26 weeks)	Type 2	IGlar versus NPH	At 26 weeks:
				• Mean HbA1c
				  - Decreased from 8.9% to 7.8 % in IDet and from 8.8% to 7.8% in NPH
				• Mean fasting plasma glucose
				  - Decreased from 10.8 ± 3.5 to 8.8 ± 2.7 mmol/L in IDet and from 10.1 mmol/L to 8.9 ± 3.1 mmol/L in NPH

Footnote:

WMD: Weighted Mean Difference

Quality of life (QoL)

None of the included systematic reviews and RCTs reported on QoL for insulin detemir treatment in type 1 diabetes mellitus.

Body weight

A systematic review and meta-analysis by Monami *et al.* involving eight studies reported a significantly smaller weight gain in the detemir group in comparison with NPH insulin by 0.26 kg/m^2 (95% CI: 0.06 to 0.47 kg/ m^2, p = 0.012).[53 level I] Similarly, Szypowska *et al.* reported a smaller body weight gain [WMD (95% CI)= -0.779 kg (-0.992 to -0.567 kg), p < 0.001)] in patients using insulin detemir compared with NPH insulin.[51 level I] A 32-week, randomised crossover design trial undertaken in 23 adult patients by Zachariah *et al.* demonstrated that after 16 weeks, weight change [Mean ± Standard error (SE)] was -0.69 kg ± 0.39 kg with insulin detemir and +1.7 kg ± 0.52 kg with NPH insulin, p < 0.001. They also found that the reduced weight gain with insulin detemir compared with NPH insulin was attributed to reduced energy intake rather than energy expenditure.[50 level II-I] In children, the change in weight standard deviation score standardised by age and gender was -0.17 kg with insulin detemir and +0.03 kg with NPH insulin.[52 level II-I]

ii. Type 2 diabetes mellitus

Glycaemic control

Two HTA reports (Tran *et al.*, Waugh *et al.*) and two systematic reviews (Singh *et al.*, Horvath *et al.*) reported similar HbA1c values for type 2 diabetes patients treated with insulin detemir compared with NPH insulin as shown in Table 6.[33,40,45-46 level I] Fajardo *et al.* conducted a 26-week, parallel-group, randomised controlled trial comparing once-daily insulin detemir with NPH insulin regimens in 277 obese or overweight patients with type 2 diabetes mellitus also found similar reduction in HbA1c values in both treatment groups. [54 level II-I]

Quality of life (QoL)

None of the included systematic reviews and RCTs reported on QoL for insulin detemir treatment in type 2 diabetes mellitus.

Body weight

Waugh *et al.* reported that the detemir groups (4 studies) gained 1.20 kg less weight than the NPH groups (range -0.8 to -1.6 kg). However, meta-analysis could not be performed due to too many missing standard deviations.[46 level I] Fajardo *et al.* also found that weight had increased significantly less with insulin detemir (0.4 kg) than with NPH (1.9 kg). Baseline-adjusted between-treatment difference was 1.5 kg (95% CI: 0.8 to 2.8 kg, p ≤ 0.0001).[54 level II-I]

iii. Gestational diabetes mellitus and pregnant women with type 1 diabetes

This review did not include any HTA report, systematic review or RCT reporting on the efficacy or effectiveness of treatment with insulin detemir compared with NPH insulin in pregnant women with type 1 diabetes and gestational diabetes mellitus.

c) Insulin glargine, insulin detemir

Systematic review and meta-analysis by Monami *et al.* described the findings of efficacy or effectiveness of insulin glargine together with insulin detemir in comparison with NPH insulin for treatment of type 1 diabetes mellitus patients. The review found that long-acting insulin analogues (insulin glargine and insulin detemir) had a small, but significant effect on HbA1c [overall standardised mean difference (95% CI): -0.07%(-0.13 to -0.011%), p = 0.026)] in comparison with NPH insulin.[53 level I]

6.1.3. Premixed insulin analogues

A systematic review (Qayyum *et al.*) and three RCTs (Gao *et al.*, Li *et al.*, Balaji *et al.*) were included in comparing premixed insulin analogues with premixed human insulin.

Qayyum *et al.* reported that premixed insulin analogues were more effective in lowering postprandial blood glucose in type 2 diabetes mellitus patients. However, premixed insulin analogues appeared to be similar in lowering HbA1c as shown in Table 7. Insulin aspart 70/30 was more effective in lowering postprandial glucose [pooled mean difference (95% CI) = -18.5 mgl/dL (-31.1 to -6.0 mg/dL)], but was less effective than premixed human insulin 70/30 in lowering fasting glucose. Insulin aspart 70/30 and premixed human insulin were similar in their ability to lower HbA1c [MD (95% CI) = 0.06% (-0.04 to 0.16%)].[55 level I]

Insulin lispro 75/25 was similar to premixed human insulin in lowering HbA1c and fasting glucose, but more effective in lowering postprandial blood glucose [pooled mean difference (95% CI) = -17.8 mg/dL (-27.0 to -8.6 mg/dL)]. Insulin lispro 50/50 was found to be less effective than premixed human insulin in lowering HbA1c and fasting glucose, but was more effective in lowering postprandial glucose [pooled MD (95% CI) = -30.3 mgl/dL (-55.6 to -5.0 mg/dL)].[55 level I]

Gao *et al*. conducted a multicentre, randomised, open-label, crossover comparison of insulin lispro mix 50 with human insulin mix 50 in type 1 and type 2 diabetes mellitus patients. They found the decrease in two-hour postprandial blood glucose (PPBG) excursion was significantly greater with insulin lispro mix 50 when compared to that of human insulin insulin mix 50 (p < 0.001).The mean two-hour PPBG excursion decreased from 6.32 ± 3.07 mmol/L at baseline to 3.47 ± 3.00 mmol/L at end-point in the insulin lispro mix 50, while it decreased from 6.31 ± 2.88 mmol/L at baseline to 5.02 ± 3.32 mmol/L at end-point in the human insulin mix 50. Both treatment groups were equivalent for HbA1c control.[56 level I]

In another multicentre, randomised, open-label, crossover study, Li *et al.* evaluated the use of twice daily insulin lispro low mix 25 compared with twice daily human insulin mix 30/70 in patients with type 1 or type 2 diabetes mellitus patients. They found similar reduction in HbA1c and FBG in both treatment groups.[57 level I] The efficacy, safety, foetal and perinatal outcomes in pregnancies associated with gestational diabetes mellitus treated with premixed insulin aspart 30 (BiAsp 30) compared with premixed human insulin 30 (BHI 30) was evaluated by Balaji *et al.* They found no statistical difference between the two groups in glycaemic control before confinement as shown in Table 7. The authors mentioned that the pregnant women found BIAsp 30 convenient as this preparation allows flexibility in the meal time insulin dosing and did not disturb their routine life pattern.[58 level I]

Table 7. Summary of glycaemic efficacy / effectiveness for premixed insulin analogues in type 1, type 2 and gestational diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Qayyum (2008)	Systematic review and meta-analysis (Database until Feb. 2008)	Type 2	Insulin aspart 70/30 versus premixed human insulin	• HbA1c [MD (95% CI) = 0.06% (-0.04 to 0.16%)] • Fasting blood glucose [MD (95% CI) = 8.33 mg/dL (0.16 to 16.49 mg/dL] • Postprandial glucose [MD (95% CI) = -18.5 mg/dL (-31.1 to -6.0 mg/dL)]
			Insulin lispro 75/25 versus premixed human insulin	• HbA1c Mean difference from three studies ranged from -0.12% to 0.2% • Fasting blood glucose [MD (95% CI) = 0.12 mg/dL (-6.05 to 6.29 mg/dL] • Postprandial glucose [MD (95% CI) = -17.8 mg/dL (-27.0 to -8.6 mg/dL)]
			Insulin lispro 50/50 versus premixed human insulin	• HbA1c May be less effective than premixed human insulin in two studies • Fasting blood glucose May be less effective than premixed human insulin • Postprandial glucose [MD (95% CI) = -30.3 mg/dL (-55.6 to -5.0 mg/dL)

Gao (2008)	Multicentre, randomised, controlled, open-label, crossover study (Study period = 24 weeks)	Type 1 and Type 2	Lispro mix 50 versus human insulin mix 50	At the end of the study:
				• HbA1c
				  - Mean HbA1c was 7.59% (decreased by 0.48%) from baseline with LM50 and 7.61% (decreased 0.46% from baseline) with human insulin mix.
				• Fasting blood glucose
				  - Mean fasting blood glucose was higher in patients with LM50 than in those on premixed human insulin (p=0.023)
				• Postprandial glucose (PPBG)
				  - 2-hour PPBG (p=0.004) and 1-hour PPBG excursion (p< 0.001) were lower with LM50 than with human insulin mix.

Li (2009)	Multicentre, randomised, open-label, crossover study (Study period = 24 weeks)	Type 1 and Type 2	Insulin lispro low mix 25 versus Human insulin mix 30/70	At the end of the study:
				• HbA1c
				  - Adjusted mean difference between the two treatments after 12 weeks was -0.05% (95% CI: -0.20 to 0.10%)
				• Fasting blood glucose
				  - No statistically significant difference (p= 0.4190) in change from baseline to endpoint FBG was observed between the two treatments

Balaji (2010)	Multicentre, parallel-group, open label RCT	Gestational diabetes	BiAsp 30 versus BHI 30	• At the end of study:
				• HbA1c (Mean ± SD) Glycaemic control (HbA1c before confinement):-
				  - BIAsp 30 (5.98 % ± 0.52% mmol/L)
				  - BHI 30 (6.04 % ± 0.61%),
				  - Mean difference between BIAsp 30 and BHI 30, p>0.05

Footnote:

MD: Mean Difference

6.2.   Safety

6.2.1. Rapid-acting insulin analogues

a) Insulin Lispro

The safety of insulin lispro compared with regular human insulin was reported by Barnajee *et al.*, Singh *et al.*, and Brunetti *et al.*[32,33,35] Barnajee *et al.* described the variations in reporting the hypoglycaemia data. When hypoglycaemia was expressed as an episode rate, the WMD was calculated. When hypoglycaemia was expressed in terms of number of patients having episodes, the relative risk (RR) was calculated.

i. Type 1 diabetes mellitus

Hypoglycaemia

In adults, compared with regular human insulin, the use of insulin lispro resulted in a lower risk for nocturnal hypoglycaemia by 49%, [RR (95% CI) = 0.51(0.42 to 0.62)] as shown in Table 8.[32,33 level I]

The risk for severe hypoglycaemia was also found to be lower by 20% in the lispro group [RR (95% CI) = 0.80 (0.67 to 0.96)].[33 level I] However, there were no differences between groups in the rate of overall hypoglycaemia.[32 level I,35 level II-I] In adolescents, the risk for nocturnal hypoglycaemia was found to be lower by 39% in the lispro group compared with regular human insulin, [RR (95% CI) = 0.61 (0.57 to 0.64)].[33 level I]

ii. Type 2 diabetes mellitus

Hypoglycaemia

For type 2 diabetes mellitus, the risk for nocturnal hypoglycaemia was found to be lower in the lispro group when two trials involving 1,570 patients were pooled, [WMD (95% CI) = -0.24 (-0.39 to -0.08)]. However, the risk for nocturnal hypoglycaemia was found to be similar in both treatment groups in one trial involving 178 patients.[32-33 level I] There were no statistically significant differences in the risk for overall and for severe hypoglycaemia.[32-33 level I]

Table 8. Summary of the risk of hypoglycaemia for insulin Lispro in type 1 and type 2 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Barnajee (2007)	Systematic review and meta-analysis (Database until Jan. 2006)	Type 1	ILis (or ILismix) versus HI (or HIMix)	• Overall hypoglycaemia (19 trials, 5,795 patients) Results not pooled, I^2=93.1%, 16 trials reported no significant difference • Severe hypoglycaemia (16 trials, 2,543 patients) [RR (95% CI) = 0.77 (0.47 to 1.27)] • Nocturnal hypoglycaemia (4 trials, 2,543 patients) [WMD (95% CI) = -0.55 (-0.92 to -0.19)]
		Type 2		• Overall hypoglycaemia (7 trials, 2,762 patients) [WMD (95% CI) = -0.16 (-0.39 to 0.07)] • Overall hypoglycaemia (3 trials, 384 patients) [RR (95% CI) = 1.24 (0.90 to 1.71)] • Severe hypoglycaemia (2 trials, 1,622 patients) [RR (95% CI) = 0.43 (0.08 to 2.37)] • Nocturnal hypoglycaemia (2 trials, 1,570 patients) [WMD (95% CI) = -0.24 (-0.39 to -0.08)] • Nocturnal hypoglycaemia (1 trial, 178 patients) [RR (95% CI) = 1.63 (0.71 to 3.73)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 1(adult)	ILis versus RHI	• Severe hypoglycaemia (10 trials, 4,502 patients) [RR (95% CI) = 0.80 (0.67 to 0.96)] • Nocturnal hypoglycaemia (4 trials, 725 patients) [RR (95% CI) = 0.51 (0.42 to 0.62)]
		Type 1 (children and adolescents)		• Severe hypoglycaemia (children, 3 trials, 222 patients) [RR (95% CI) = 0.69 (0.24 to 2.01)] • Nocturnal hypoglycaemia (children, 3 trials, 234 patients) [RR (95% CI) = 0.96 (0.74 to 1.26)] • Severe hypoglycaemia (adolescents, 1 trial, 926 patients) [RR (95% CI) = 1.00 (0.29 to 3.43)] • Nocturnal hypoglycaemia (adolescents, 1 trial, 926 patients) [RR (95% CI) = 0.61 (0.57 to 0.64)]
		Type 2 (adult)		• Severe hypoglycaemia (2 trials, 1,622 patients) [RR (95% CI) = 0.43 (0.08 to 2.37)] • Nocturnal hypoglycaemia (1 trial, 178 patients) [RR (95% CI) = 1.63 (0.71 to 3.73)]
Brunetti (2010)	Multicentre, parallel-group, open label RCT (Study period=28 weeks)	Type 1	Insulin glargine and insulin lispro versus insulin glargine and RHI	At the end of study: • Severe nocturnal hypoglycaemia - Three (1.55%) in the RHI group versus 2 (1.11%) in the lispro group, p=0.938, mean difference was 0.44% (95% CI: -1.77 to 2.21%) - Overall incidence 0.015 versus 0.016 episodes /patient/ month for the RHI and lisro group respectively, p= 0.924 • Overall hypoglycaemia: - No difference in the incidence of overall hypoglycaemia between the two groups (2.85 versus 2.85 episodes / patient / month, respectively)

Footnote:

MD: Mean Difference, **RR:** Relative Risk

b) Insulin aspart

One HTA report, two systematic reviews and three RCTs evaluated the safety of insulin aspart compared with regular human insulin.

i. Type 1 diabetes mellitus

Hypoglycaemia

The summary of hypoglycaemia findings for insulin aspart is shown in Table 9. Systematic reviews by Singh *et al.* and Rys P *et al.* reported that treatment with insulin aspart resulted in lower risk for nocturnal hypoglycaemia by 45%, [RR (95% CI) = 0.55 (0.43 to 0.70)] and by 33% [RR (95% CI) = 0.67 (0.54 to 0.83)] respectively.[33,36 level I] However, there were no differences between groups in the risk for severe hypoglycaemia or the rate of overall hypoglycaemia.

ii. Type 2 diabetes mellitus

Hypoglycaemia

There were no differences in the risk of nocturnal, severe or overall hypoglycaemia between the two treatment groups.[32-33,36 level I]

Adverse events (excluding hypoglycaemia episodes)

The adverse events reported for rapid-acting insulin analogues (insulin lispro, insulin aspart, insulin glulisine) were headache, pharyngitis, rhinitis, upper respiratory infection, flu syndrome, pain and injection site reactions. Most were judged to be unrelated to treatment and the incidence of adverse events was similar between rapid-acting insulin analogues and conventional insulin.[32 level I]

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Table 9. Summary of the risk of hypoglycaemia for insulin aspart in type 1, type 2, pregnant women with type 1 diabetes mellitus and gestational diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Barnajee (2007)	Systematic review and meta-analysis (Database until Jan. 2006)	Type 1 Type 2	IAsp (or IAspMix) versus HI (or HIMix)	• Hypoglycaemia (14 trials) Patients in IAsp and HI group had the same incidence rate for overall, severe and nocturnal hypoglycaemia • Hypoglycaemia (5 trials, 987 patients) No significant difference for overall, severe, and nocturnal hypoglycaemia
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 1(adult) Type 2	IAsp versus RHI	• Severe hypoglycaemia (4 trials, 1,814 patients) [RR (95% CI) = 0.83 (0.65 to 1.04)] • Nocturnal hypoglycaemia (1 trial, 118 patients) [RR (95% CI) = 0.55 (0.43 to 0.70)] • Severe hypoglycaemia (1 trial, 121 patients) [RR (95% CI) = 0.39 (0.11 to 1.36)] • Nocturnal hypoglycaemia (1 trial, 93 patients) [RR (95% CI) = 0.65 (0.28 to 1.53)]
Rys P (2011)	Systematic review and meta-analysis (Database until July 2009)	Type 1 Type 2	IAsp (or BiAsp) versus HI (or biphasic human insulin)	• All hypoglycaemia (4 studies, 2,220 patients) [RR (95% CI) = 1.06 (1.01 to 1.10)] • Severe hypoglycaemia (7 studies, 2,358 patients) [RR (95% CI) = 0.92 (0.75 to 1.12)] • Nocturnal hypoglycaemia (3 studies, 2,065 patients) [RR (95% CI) = 0.67 (0.54 to 0.83)] • All hypoglycaemia (5 studies, 882 patients) [RR (95% CI) = 1.04 (0.92 to 1.17)] • Severe hypoglycaemia (2 studies, 206 patients) [RR (95% CI) = 0.67 (0.17 to 2.53)] • Nocturnal hypoglycaemia (1 study, 93 patients) [RR (95% CI) = 0.65 (0.28 to 1.48)]
Mathiesen (2007)	Multicentre, parallel group, open-label RCT Study period = maximum duration 22 months	Pregnant women with type 1 diabetes	IAsp versus RHI	• Major maternal hypoglycaemia RR (95% CI) = 0.72 (0.36 to 1.46)] • Major nocturnal maternal hypoglycaemia RR (95% CI) = 0.48 (0.42 to 1.14)] • Major daytime maternal hypoglycaemia RR (95% CI) = 0.85 (0.40 to 1.78)] • Any nocturnal maternal hypoglycaemia RR (95% CI) = 0.76 (0.57 to 1.03)]
Pettit (2007)	Single centre, parallel group, open-label RCT Study period= from 18 to 28th week of pregnancy to 6 weeks postpartum	Gestational diabetes	IAsp versus RHI	• Hypoglycaemic episodes: Symptomatic hypoglycaemic episodes reported by 19 subjects (10 in IAsp group and 9 in RHI group) • No hypoglycaemic episodes required assistance of another person

Footnote:

RR: Relative Risk

iii. Gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus

Hypoglycaemia

Mathiesen *et al.* demonstrated that the rate of major maternal hypoglycaemia and major nocturnal maternal hypoglycaemia in pregnant women with type 1 diabetes mellitus were lower with the insulin aspart than regular human insulin but did not reach statistical significance as shown in Table 9.[37] level II-I Pettit *et al.* found similar rate of symptomatic hypoglycaemic episodes in gestational diabetes treated with insulin aspart and regular human insulin. No hypoglycaemic episodes required assistance of another person.[38] level II-I

Perinatal and foetal outcomes

Pettit *et al.* reported that pregnancy outcomes in pregnant women with gestational diabetes (determined by neonatal assessment: weight, length, physical examination findings) were similar in both treatment groups.[38] level II-I Similarly, in pregnant women with type 1 diabetes mellitus Hod *et al.* found no difference in foetal or perinatal outcomes between the insulin aspart and regular human insulin treatment groups with respect to foetal loss, perinatal mortality, congenital malformation, and neonatal short-term complications.[59] level II-I

Adverse events

In the study by Mathiesen *et al.*, no maternal deaths were reported and both insulins were well tolerated and the adverse event profiles were similar. They also found that most events were mild or moderate and considered unlikely to be related to the study products. Pettit *et al.* reported that in both treatments groups the most frequently reported adverse events were upper respiratory tract infections. The investigators considered fatigue (one subject) and somnolence (one subject) and injection site reactions [insulin aspart (one subject) and regular human insulin (two subjects)] to be the only adverse events possibly or probably related to the study drug.[37-38] level II-I

c) Insulin glulisine

Systematic review by Barnajee *et al.* reported that there were no significant differences between treatments (insulin glulisine versus regular human insulin) for symptomatic and nocturnal hypoglycaemia for type 1 diabetes mellitus. For type 2 diabetes mellitus, the risk for overall, severe and nocturnal hypoglycaemia were similar for insulin glulisine or insulin glulisine mix and regular human insulin or human insulin mix.[32] level I

d) Insulin lispro, insulin aspart, insulin glulisine

A systematic review by Siebenhofer *et al.* described the findings of the three rapid-acting insulin analogues together (insulin lispro, insulin aspart, insulin glulisine) while Plank *et al.* conducted a systematic review on two rapid-acting insulin analogues together (insulin lispro, insulin aspart) compared with regular human insulin.[34,39]

Table 10. Summary of the risk of hypoglycaemia for rapid-acting insulin analogues (insulin lispro, insulin aspart, insulin glulisine) in type 1, type 2, pregnant women with type 1 diabetes mellitus and gestational diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Siebenhofer (2006, edited 2009)	Systematic review and meta-analysis (Database until 2005)	Type 1 (adult)	Rapid-acting insulin analogues (ILis, IAsp, Insulin glulisine) versus RHI	• Overall hypoglycaemia (10 studies, 4,266 patients) [WMD (95% CI) = -0.23 (-1.14 to 0.69)] • Severe hypoglycaemia 　- Ranged from 0 to 137.3 (median 21.8) episodes per 100 person-years for insulin analogues 　- Ranged from 0 to 544 (median 46.1) episodes per 100 person-years for regular insulin
		Type 1 (children and (adolescents)		• Overall rate of hypoglycaemic episodes per patient per 30 days- did not significantly differ in prepubertal children • Hypoglycaemic episodes per patient per 30 days- significantly reduced with insulin analogue (P=0.02) in adolescents • Severe hypoglycaemic episodes- did not significantly differ in prepubertal children and adolescents
		Type 2		• Overall hypoglycaemia (5 studies, 2,617 patients) [WMD (95% CI) = -0.17 (-0.46 to 0.12)] • Severe hypoglycaemia 　- Ranged from 0 to 30.3 (median 0.3) episodes per 100 person-years for insulin analogues 　- Ranged from 0 to 50.4 (median 1.4) episodes per 100 person-years for regular insulin
		Pregnant type 1 diabetes		• Event rate regarding biochemical hypoglycaemia was significantly higher in the analogue group compared to the regular group (P<0.05).
		Gestational diabetes		• Total number of hypoglycaemic events was lower in the lispro group but not significant.
Plank (2005)	Systematic review and meta-analysis (Database until Dec. 2003)	Type 1 (adult)	Rapid-acting insulin analogues (ILis, IAsp) versus RHI	• Overall hypoglycaemia [SMD (95% CI) = -0.05 (-0.22 to 0.11)]
		Type 2		• Overall hypoglycaemia [SMD (95% CI) = -0.17 (-0.12 to 0.04)]
		Type 1 (children and adolescents)		• Overall rate of hypoglycaemic episodes per patient per month did not significantly differ in prepubertal children in either of the studies • Overall rate of hypoglycaemic episodes per patient per month was significantly reduced with insulin analogue group (P<0.02)
		Pregnant type 1 diabetes		• Event rate regarding biochemical hypoglycaemia was significantly higher in the analogue group compared with the regular group (P<0.05)
		Gestational diabetes		• In one study, the total number of hypoglycaemic events did not differ between groups

Footnote:

WMD: Weighted Mean Difference, **SMD:** Standardized Mean Difference

Hypoglycaemia

The overall hypoglycaemia was similar between the two treatment groups for adult and children with type 1 diabetes mellitus or for type 2 diabetes mellitus as shown in Table 10.[34,39 level I] However, in adolescents with type 1 diabetes mellitus, the hypoglycaemic episodes per patient per month was significantly reduced with rapid-acting insulin analogues (p = 0.02).[34,39 level I] For pregnant women with type 1 diabetes mellitus, the event rate regarding biochemical hypoglycaemia was significantly higher in the rapid-acting insulin analogues compared with regular human insulin (p < 0.05).[34,39 level I]

Adverse events

Overall, frequency and type of adverse events were reported to be comparable for the two treatment groups.[34,39 level I] Most of the events were mild in severity, such as respiratory tract infections, headaches, fly symptoms or accidental injuries and were not considered to be related to one of the treatments.[34 level I]

6.2.2. Long-acting insulin analogues

a) Insulin glargine

Three HTA reports, six systematic reviews and five RCTs were included in this review to compare the safety of insulin glargine with NPH insulin.

i. Type 1 diabetes mellitus

Hypoglycaemia

The risk of hypoglycaemia for insulin glargine in type 1 diabetes mellitus is summarised in Table 11. There were no statistically significant differences in the risk for overall, severe and nocturnal hypoglycaemia in adults, children and adolescents with type 1 diabetes mellitus treated with insulin glargine compared with NPH insulin.[33,40,41 level I, 42-43 level II-I] In the RCT by Bolli *et al.* there was a significant decrease in serious nocturnal hypoglycaemia (blood glucose < 42 mg/dL) in the glargine group from baseline to endpoint [mean ± 95% CI = -0.19(-0.32 to -0.05), p = 0.006] but not in the NPH insulin group [mean ± 95% CI = -0.10 (-0.24 to 0.03), p = 0.123].[42 level II-I]

Adverse events

Warren *et al.* reported the most common treatment-emergent adverse reaction was injection site pain.[41 level I] There was no significant difference in the number of adverse events reported by both treatment groups. One patient in each of the two groups experienced drug related adverse events (in the glargine group consisted of hypoglycaemia due to error in the glargine administration, while in the NPH group consisted of bilateral micro-aneurysm and none of the adverse events caused early study discontinuation).[42 level II-I] Similarly, Chase *et al.* reported no difference between the two treatment groups in the overall reported incidence of adverse events (p= 0.1944).They found both treatments were safe and tolerable, with only one patient in the insulin glargine group and two patients in the NPH/Lente group discontinuing due to an adverse event.[43 level II-I]

Table 11. Summary of the risk of hypoglycaemia for insulin glargine in type 1 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Tran (2007)	Systematic review and meta-analysis (Database until Feb. 2006)	Type 1	IGlar versus NPH	• Overall hypoglycaemia (8 trials, 2,996 patients) [RR (95% CI) = 1.00 (0.47 to 1.06)] • Severe hypoglycaemia (6 trials, 2,701 patients) [RR (95% CI) = 0.78 (0.58 to 1.05)] • Nocturnal hypoglycaemia (7 trials, 2,826 patients) [RR (95% CI) =0.92 (0.81 to 1.04)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 1 (adult) Type 1 (children and adolescents)	IGlar versus NPH	• Severe hypoglycaemia (7 trials, 2,227 patients) [RR (95% CI) = 0.82 (0.52 to 1.29)] • Nocturnal hypoglycaemia (5 trials, 1,943 patients) [RR (95% CI) = 0.97 (0.87 to 1.09)] • Severe hypoglycaemia (children and adolescents, 4 trials, 727 patients) [RR (95% CI) = 1.18 (0.59 to 2.35)] • Nocturnal hypoglycaemia (children and adolescents, 1 trial, 349 patients) [RR (95% CI) = 0.71 (0.43 to 1.18)]
Warren (2004)	Systematic review (Database until 2002)	Type 1	IGlar versus NPH	• There is not enough evidence to conclude that insulin glargine is superior to NPH in controlling either symptomatic or severe hypoglycaemia.

Bolli (2009)	Multicentre, parallel-group, open label RCT (Study period=30 weeks)	Type 1	IGlar versus NPH	Baseline to endpoint change:
				
				• Overall hypoglycaemia (Mean ± 95% CI)
				   - Insulin glargine group =[0.26 (-0.84 to 1.35)]
				   - Insulin NPH group = [0.21 (-0.87 to 1.29)]
				
				• Serious hypoglycaemia (Mean ± 95% CI)
				   - Insulin glargine group =[-0.54 (-0.97 to -0.10)]
				   - Insulin NPH group = [-0.54 (-0.97 to -0.11)]
				
				• Serious nocturnal hypoglycaemia (Mean± 95% CI)
				   - Insulin glargine group =[-0.19 (-0.32 to -0.05)]
				   - Insulin NPH group = [-0.10 (-0.24 to 0.03)]

Chase (2008)	Parallel-group, open label RCT among adolescents (Study period=24 weeks)	Type 1	IGlar versus NPH/Lente	• The rate of confirmed glucose values <70 mg/dL was higher in patients receiving insulin glargine (p = 0.0298) • No significant difference in the rates of severe hypoglycaemia (p = 0.1814), or occurrence of glucose levels < 50 mg/dL (p = 0.82) or < 36 mg/dL(p = 0.32)

Footnote:
RR: Relative Risk

Table 12. Summary of the risk of hypoglycaemia for insulin glargine in type 2 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Tran (2007)	Systematic review and meta-analysis (Database until Feb. 2006)	Type 2	IGlar versus NPH	• Overall hypoglycaemia (6 trials, 2,211 patients) [RR (95% CI) = 0.89 (0.83 to 0.96)] • Severe hypoglycaemia (4 trials, 1,885 patients) [RR (95% CI) = 1.09 (0.56 to 2.12)] • Nocturnal hypoglycaemia (5 trials, 2,099 patients) [RR (95% CI) = 0.57 (0.44 to 0.74)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 2	IGlar versus NPH with oral antidiabetic therapy in both arms	• Severe hypoglycaemia (7 trials, 2,866 patients) [RR (95% CI) = 0.66 (0.29 to 1.48)] • Nocturnal hypoglycaemia (7 trials, 2,532 patients) [RR (95% CI) = 0.56 (0.47 to 0.68)]
Warren (2004)	Systematic review (Database until 2002)	Type 2	IGlar versus NPH	• There is not enough evidence to conclude that insulin glargine is superior to NPH in controlling either symptomatic or severe hypoglycaemia.
Horvath (2007, edited 2009)	Systematic review and meta-analysis	Type 2	IGlar versus NPH	• Symptomatic hypoglycaemia (3 studies, 1,458 patients) [Peto-OR (95% CI) = [0.84 (0.75 to 0.95)] • Severe hypoglycaemia (4 studies, 2,207 patients) [Peto-OR (95% CI) = [0.70 (0.40 to 1.23)] • Nocturnal hypoglycaemia (5 studies, 2,099 patients) [Peto-OR (95% CI) = [0.66 (0.55 to 0.80)]
Waugh (2010)	Systematic review and meta-analysis (Database until April 2008)	Type 2	IGlar versus NPH	• Overall hypoglycaemia (7 trials, 2,297 patients) [RR (95% CI) = [0.89 (0.83 to 0.96)] • Symptomatic hypoglycaemia (4 trials, 1,662 patients) [RR (95% CI) = [0.80 (0.68 to 0.93)] • Severe hypoglycaemia (6 trials, 2,916 patients) [RR (95% CI) = [0.82 (0.45 to 1.49)] • Nocturnal hypoglycaemia (7 trials, 2,678 patients) [RR (95% CI) = [0.54 (0.43 to 0.69)]
Bazzano (2008)	Systematic review and meta-analysis (Database until March 2007)	Type 2	IGlar versus NPH	Mean percentage of participants reporting hypoglycaemia (NPH versus Glargine): • Anyl hypoglycaemia (10 trials) (58.95% versus 53.01%, p<0.0003) • Symptomatic hypoglycaemia (6 trials) (51.40% versus 42.88%, p<0.0001) • Severe hypoglycaemia (7 trials) (2.5% versus 1.4%, p=0.07) • Nocturnal hypoglycaemia (9 trials) (33.25% versus 19.10%, p<0.0001)
Mu (2011)	Open label RCT (Study period =3 months)	Type 2	IGlar versus NPH	• Hypoglycaemic Incidence was not significantly lower in the insulin glargine group [6 of 124 (4.84%)] than in the NPH group [9 of 126 (7.14%)] • No severe hypoglycaemic episodes occurred during the study period
Mattia (2009)	Randomised, open-label, single centre, two way cross-over study (Study period = 27 weeks)	Type 2	IGlar plus OADs versus NPH plus OADs	• Overall Incidence of hypoglycaemia: - Insulin glargine = 1.04 episodes/patient/per month - NPH insulin = 2.12 episodes/patient/per month
Rosenstock (2009)	5 year, multicentre, multinational, open-label, randomised parallel-group study	Type 2	IGlar versus NPH	Patients mean yearly rate of hypoglycaemia (Mean ± SD): • Symptomatic hypoglycaemia - Insulin glargine group = 5.13 ± 12.79 - Insulin NPH group = 7.08 ± 16.49, - Mean difference between two groups = 0.0017

Footnote:
RR: Relative Risk, **OR:** Odds Ratio

ii. Type 2 diabetes mellitus

Hypoglycaemia

In type 2 diabetes mellitus patients, two HTA reports and three systematic reviews demonstrated that the risk of nocturnal hypoglycaemia was significantly lower in patients treated with insulin glargine compared with NPH insulin by 34% to 46% as shown in Table 12.[33,40,46-47 level I]

Home *et al.* conducted a systematic review and meta-analysis of randomised controlled open-label studies with accessible patient data (IPD) to estimate absolute and relative incidence rates of hypoglycaemia when using once-daily evening (pool 1) or morning regimens (pool 2) of insulin glargine versus once-daily evening NPH insulin. In study pool 1 (n=2,711), the risk of all severities of nocturnal hypoglycaemia was approximately halved with glargine compared with NPH [(OR): 0.44 to 0.52, p <0.001 to 0.047]. In study pool 2 (n=470), although a strong numerical reduction in all types of nocturnal hypoglycaemia was observed (OR: 0.16 to 0.064), statistical significance was reached only for symptomatic hypoglycaemia with plasma glucose < 3.9 mmol/L, p < 0.001. In study pool 1, the number needed to treat (NNT) with glargine versus NPH for symptomatic hypoglycaemia with plasma glucose < 3.9 mmol/L was eight and for study pool 2, the NNT was five. Eight (pool 1) or five (pool 2) people with type 2 diabetes mellitus needed to use glargine rather than NPH to avoid one person from experiencing a nocturnal symptomatic hypoglycaemic event within a median of about 25 weeks of starting insulin.[60 level I]

Overall hypoglycaemia was also found to be significantly lower by 11% in patients treated with insulin glargine compared with NPH insulin.[40,46 level I] Similarly, the risk for symptomatic hypoglycaemia was also found to be significantly lower in the insulin glargine group.[45-47 level I,61 level II-I]

Adverse events

Horvath *et al.* reported that the numbers of adverse events and numbers of patients withdrawing due to adverse events were comparable between treatment groups.[45 level I] Similarly, Waugh *et al.* also reported no significant differences in adverse events, number of patients with adverse events, severe adverse events, or withdrawals because of adverse events between insulin glargine or detemir and NPH insulin.[46 level I] Mattia *et al.*, reported three patients experienced at least one adverse event during treatment with insulin glargine. However, none of the events was considered to be related to study drug.[49 level I]

The long-term safety of insulin glargine compared with NPH insulin was evaluated by Rosenstock *et al.* The main objective of the study was to compare the progression of diabetic retinopathy between treatment groups by analysing the percentage of patients with three or more steps progression in the Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale based on the masked, centralised grading of seven-field stereoscopic fundus photographs. They found that despite a slightly greater severity of diabetic retinopathy for insulin glargine group at baseline, three of more step progression in EDTRS score from baseline to end-of-study was similar between treatment groups (14.2% of insulin glargine treated patients versus 15.7% of NPH insulin treated patients). The difference in the incidence of progression was -1.98% (95% CI:-7.02 to 3.06%). Other measures of retinopathy; the development of proliferative diabetic retinopathy and progression to clinically significant macular oedema occurred to a similar degree in both treatment groups. No other safety issues, such as unexpected adverse events for either insulin emerged during the five year study.[61 level II-I]

iii. Gestational diabetes mellitus and pregnant women with diabetes

Foetal safety

The foetal safety of insulin glargine compared with NPH insulin therapy for the treatment of diabetes in pregnancy was investigated by Pollex *et al.* through a systematic review and meta-analysis. Eight observational cohort studies involving 702 women with pregestational or gestational diabetes in pregnancy treated with either insulin glargine (n = 331) or NPH insulin (n = 371) were included. They found no statistically significant differences in the occurrence of foetal or neonatal outcomes studied (large for gestational age, macrosomia, neonatal hypoglycaemia, NICU admissions, shoulder dystocia, congenital anomalies, preterm delivery, perinatal mortality, hyperbilirubinaemia and respiratory distress) with the use of insulin glargine compared to NPH insulin.[62 level II-I]

b) Insulin detemir

In comparing the safety of insulin detemir with NPH insulin, two HTA reports, three systematic reviews and three RCTs were included in this review.

i. Type 1 diabetes mellitus

Hypoglycaemia

In adults with type 1 diabetes mellitus, one HTA report and two systematic reviews showed a statistically significant lower risk for severe hypoglycaemia by 25% to 34% with use of insulin detemir as shown in Table 13.[40,33,51 level I] Similarly, the risk for nocturnal hypoglycaemia was also significantly reduced by 8% to 13%.[40,33,51 level 1] Tran *et al.* and Zachariah *et al.* reported similar overall hypoglycaemia in the two groups.[40 level I, 50 level II-I] In contrast, a newer systematic review by Syzpowska *et al.* reported lower overall hypoglycaemia in patients treated with insulin detemir, [RR (95% CI) = 0.978 (0.961 to 0.996)].[51 level I]

In children and adolescents with type 1 diabetes mellitus, the risk for nocturnal hypoglycaemia was statistically significantly lower by 15% in the insulin detemir group [RR (95% CI) = 0.85 (0.77 to 0.94)], while severe hypoglycaemia was similar in the two groups.[33 level I] Thalange *et al.* found that in children between two to five years, the percentage of children with hypoglycaemic episodes was similar between treatments, but children treated with insulin detemir had fewer episodes than those treated with NPH insulin as shown in Table 13.[52 level II-I]

Table 13. Summary of the risk of hypoglycaemia for insulin detemir in type 1 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Tran (2007)	Systematic review and meta-analysis (Database until Feb. 2006)	Type 1	IDet versus NPH	• Overall hypoglycaemia (7 trials, 2,437 patients) [RR (95% CI) = 0.99 (0.97 to 1.02)] • Severe hypoglycaemia (8 trials, 2,708 patients) [RR (95% CI) = 0.75 (0.59 to 0.95)] • Nocturnal hypoglycaemia (7 trials, 2,590 patients) [RR (95% CI) =0.89 (0.82 to 0.97)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 1 (adult) Type 1 (children and adolescents)	IDet versus NPH	• Severe hypoglycaemia (7 trials, 2,442 patients) [RR (95% CI) = 0.74 (0.58 to 0.96)] • Nocturnal hypoglycaemia (6 trials, 2,311 patients) [RR (95% CI) = 0.92 (0.85 to 0.98)] • Severe hypoglycaemia (children and adolescents, 1 trial, 347 patients) [RR (95% CI) = 0.80 (0.50 to 1.28)] • Nocturnal hypoglycaemia (children and adolescents, 1 trial, 347 patients) [RR (95% CI) = 0.85 (0.77 to 0.94)]
Szypowska (2011)	Systematic review and meta-analysis (Database until Nov. 2010)	Type 1	IDet versus NPH	• Overall hypoglycaemia (8 trials, 3,096 patients) [RR (95% CI) = 0.978 (0.961 to 0.996)] • Severe hypoglycaemia (8 trials, 3,149 patients) [RR (95% CI) = 0.665 (0.547 to 0.810)] • Nocturnal hypoglycaemia (8 trials, 3,304 patients) [RR (95% CI) = 0.877 (0.816 to 0.942)] • Severe nocturnal hypoglycaemia (6 trials, 2,642 patients) [RR (95% CI) = 0.687 (0.392 to 1.204)]

Thalange (2011)	Open-label, parallel group RCT (Study period=52 weeks)	Type 1 Children between 2 to 5 years	IDet versus NPH	• Severe hypoglycaemic episodes:
				  - IDet group (no severe hypoglycaemic episodes were reported)
				  - NPH group (6 episodes in three subjects)
				• Mean rate episodes per patient-year of exposure (IDet versus NPH):
				  - Total hypoglycaemic events (50.6 versus 78.3)
				  - Nocturnal (8.0 versus 17.4)

Zachariah (2011)	Randomised, single centre, open-labelled, crossover design	Type 1 (adult)	IDet versus NPH	Hypoglycaemic episodes (< 3.1 mmol/L): • No significant difference between insulin detemir (4.6 ± 1.58) versus NPH insulin (4.9 ± 1.53), p= 0.586 • No major hypoglycaemic episodes (defined as patients unable to treat themselves) in the trial

Footnote:
RR: Relative Risk

Adverse events

Thalange *et al.* found a slightly lower proportion of children in the two to five years of age reported adverse events with insulin detemir than with NPH insulin (69.0% versus 77.5%). Serious adverse events were few (five with insulin detemir and seven with NPH insulin). The most common serious adverse events were infections (gastroenteritis) and gastrointestinal disorders (dyspepsia) in both treatment groups. No deaths were reported in this trial.[52 level II-I]

ii. Type 2 diabetes mellitus

Hypoglycaemia

Two HTA reports and two systematic reviews, reported a statistically significant reduction in the risk for nocturnal hypoglycaemia by 34% to 47% as shown in Table 14.[40,46,33,45 level I.] Horvath *et al.* and Waugh *et al.* also reported a significantly lower risk for overall hypoglycaemia by 18% and 32% respectively.[45-46 level I] However, the risk for severe hypoglycaemia was found to be similar in both treatment groups.[33,45-46 level I] An RCT by Fajardo *et al.* also found a statistically significant difference in the risk for all hypoglycaemic events and nocturnal hypoglycaemic events, [RR for determir versus NPH insulin=0.62, p < 0.0001) and 0.43, (p < 0.0001) respectively]. There was no major hypoglycaemic episodes in the insulin detemir group, but there was three major hypoglycaemic episodes in the NPH insulin group.[54 level II-I]

Adverse events

Horvath *et al.* in their systematic review described that there were two studies which reported no difference in the frequency of adverse events between the insulin detemir and the NPH insulin.[45 level I] Waugh *et al.* also reported no significant differences in adverse events, number of patients with adverse events, severe adverse events, or withdrawals because of adverse events seen between insulin detemir and NPH insulin.[46 level I] A 26-week, parallel group, RCT comparing once-daily insulin detemir with NPH insulin in intensive insulin regimens in obese or overweight patients with type 2 diabetes mellitus, found that insulin detemir and NPH insulin were both well tolerated, with no major safety concerns noted and a similar incidence of adverse events in the two groups.[54 level II-I]

Table 14. Summary of the risk of hypoglycaemia for insulin detemir in type 2 diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Tran (2007)	Systematic review and meta-analysis (Database until Feb. 2006)	Type 2	IDet versus NPH	• Overall hypoglycaemia (1 trial) [RR (95% CI) = 0.91 (0.75 to 1.11)] • Nocturnal hypoglycaemia (1 trial) [RR (95% CI) = 0.66 (0.45 to 0.96)]
Singh (2009)	Systematic review and meta-analysis (Database until April 2007)	Type 2	IDet versus NPH with OADs versus NPH with OADs	• Severe hypoglycaemia (2 trials, 808 patients) [RR (95% CI) = 0.75 (0.03 to 20.01)] • Nocturnal hypoglycaemia (2 trials, 808 patients) [RR (95% CI) = 0.53 (0.31 to 0.91)]
Horvath (2007, edited 2009)	Systematic review and meta-analysis	Type 2	IDet versus NPH	• Overall hypoglycaemia (2 studies, 980 patients) [Peto-OR (95% CI) = [0.82 (0.74 to 0.90)] • Severe hypoglycaemia (2 studies, 980 patients) [Peto-OR (95% CI) = [0.50 (0.18 to 1.38)] • Nocturnal hypoglycaemia (2 studies, 980 patients) [Peto-OR (95% CI) = [0.63 (0.52 to 0.76)]
Waugh (2010)	Systematic review and meta-analysis (Database until April 2008)	Type 2	IDet versus NPH	• Overall hypoglycaemia (4 trials, 1,584 patients) [RR (95% CI) = [0.68 (0.54 to 0.86)] • Severe hypoglycaemia (4 trials, 1,584 patients) [RR (95% CI) = [0.59 (0.15 to 2.24)] • Nocturnal hypoglycaemia (4 trials, 1,584 patients) [RR (95% CI) = [0.54 (0.42 to 0.68)]

Fajardo (2008)	Open-label, parallel group RCT (study period=26 weeks)	Type 2	IDet versus NPH	• All hypoglycaemic events:
				  - IDet group (256 hypoglycaemia events were reported by 34.7% of patients)
				  - NPH insulin group (481 hypoglycaemia events were reported by 65.3% of patients)
				  - RR for detemir versus NPH insulin =0.62, (p<0.0001)
				• Nocturnal hypoglycaemic events:
				  - IDet group (46 events were reported by 30.1% of patients)
				  - NPH insulin group (107 events were reported by 69.9% of patients)
				  - RR for detemir versus NPH insulin =0.43, (p< 0.0001)
				• Major hypoglycaemic episodes:
				  - IDet group (no episodes)
				  - NPH insulin group (three episodes)

Footnote:
RR: Relative Risk, **OR:** Odds Ratio

iii. Gestational diabetes mellitus and pregnant women with diabetes mellitus

This review did not identify any HTA report, systematic review or RCT reporting on the safety of treatment with insulin detemir compared with NPH insulin in pregnant women with diabetes mellitus and gestational diabetes mellitus.

c) Insulin glargine, insulin detemir

A systematic review and meta-analysis by Monami *et al.* described the safety findings of long-acting insulin analogues together (insulin glargine and insulin detemir) versus NPH insulin in type 1 diabetes mellitus. Long-acting insulin analogues were associated with a reduced risk for nocturnal and for severe hypoglycaemia [OR (95% CI): 0.69 (0.55 to 0.86) and OR (95% CI):0.73 (0.60 to 0.89)] respectively.[53 level I]

6.2.3. Premixed insulin analogues

Hypoglycaemia

The risk of hypoglycaemia was found to be similar for premixed insulin analogues and premixed human insulin as shown in Table 15.[55 level I, 56-57 level II-I] In the study by Balaji *et al.*, no maternal hypoglycaemic episodes were observed.[58 level II-I]

Table 15. Summary of the risk of hypoglycaemia for premixed insulin analogues in type 1, type 2 and gestational diabetes mellitus

STUDY	STUDY DESIGN	DIABETES PATIENT GROUP	INTERVENTION	OUTCOME
Qayyum (2008)	Systematic review and meta-analysis (Database until Feb. 2008)	Type 2	Premix insulin analogues (insulin aspart 70/30, insulin lispro 75/25, insulin lispro 50/50) versus Premixed human insulin (NPH/regular 70/30, NPH/regular 50/50) or NPH insulin	• Premixed insulin analogues (insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50) were similar to premixed human insulin preparations in terms of the incidence of hypoglycaemia.

Gao (2008)	Multicentre, randomised, controlled, open-label, crossover study (study period =24 weeks)	Type 1 and Type 2	Lispro mix 50 versus human insulin mix 50	• Incidence of hypoglycaemia:
				  - No statistically significance difference between treatment groups (p= 0.828)
				• Rate of hypoglycaemia per 30 days:
				  - No statistically significance difference between treatment groups (p= 0.401)

Li (2009)	Multicentre, randomised, open-label, crossover study (study period = 24 weeks)	Type 1 and Type 2	Insulin lispro low mix 25 versus Human insulin mix 30/70	• No statistically significant difference (p= 0.670) in hypoglycaemia rate between the two treatments, with an adjusted mean hypoglycaemia rate of 0.34 episodes per patient per 30 days (95% CI; 0.19 to 0.49) during human insulin mix 30/70 treatment and 0.37 episodes per patient per 30 days (95% CI; 0.22 to 0.52) during insulin lispro low mix treatment.
Balaji (2010)	Multicentre, parallel-group, open label RCT	Gestational diabetes	BiAsp 30 versus BHI 30	• No maternal hypoglycaemic episodes were observed

Footnote:
RR: Relative Risk

Adverse events

Gao *et al.* reported that insulin lispro mix 50 was generally well tolerated by patients treated for three months. Three patients experienced serious adverse events requiring admission, one during insulin lispro mix 50 treatment (due to pneumonia) and two during human insulin mix 50 treatment (due to coronary artery disease and hepatitis E). However, they were regarded by investigators to have no relationship with either the study drug or device. Similar numbers of patients experienced at least one treatment-emergent adverse event (TEAEs) in each treatment group (39 in insulin lispro mix 50 and 37 in human insulin mix 50). Most common TEAEs reported by patients were nasopharyngitis followed by hyperuricaemia and hypertension.[56] level II-I

In another study, Li *et al.* reported three serious adverse events in patients with type 1 and type 2 diabetes mellitus treated with insulin lispro low mix 25 or twice daily human insulin mix 30/70. Two patients (1.7%) during human insulin mix 30/70 treatment (hypoglycaemic coma and cardiac failure) and the other one (0.9%) during insulin lispro mix 25 treatment (stroke). All serious adverse events were resolved.[57] level II-I Balaji *et al.* conducted a pilot study involving gestational diabetes mellitus patients treated with premixed insulin aspart 30 (BIAsp 30) or premixed human insulin 30 (BHI 30).They found the frequency of birth weight of new born above 90th percentile was 6.8% in the BIAsp group and 9.2 % in the BHI 30 group. The proportion of macrosomia was higher in the BHI 30 group when compared to BIAsp 30 group, however, the difference was not statistically significant. There were no adverse perinatal outcomes recorded.[58] level II-I

6.3.　Cost/ cost-efectiveness / economic evaluation

In this review, we included 13 robust cost-effectiveness studies for rapid-acting, long-acting and premixed insulin analogues. Most cost-effectiveness analyses use the IMS CORE Diabetes Model. The Model is a non product-specific diabetes policy analysis tool which takes into account intensive or conventional insulin therapy, screening and treatment strategies for microvascular complications, treatment strategies for end-stage complications and multifactorial interventions. Disease progression is based on a series of inter-dependent sub-models that simulate progression of diabetes-related complications as well as mortality from other sources. The IMS CORE Diabetes Model uses Monte Carlo simulation and non-parametric bootstrap methods to evaluate uncertainty in the cost-effectiveness outcomes. Output data in terms of development of complications, life expectancy, quality-adjusted life expectancy, direct medical costs and indirect medical costs can be projected. Other simulation models include the Diabetes Mellitus Model (DMM), and the discrete event simulation (DES) model. Table 16 provides a summary of evidence addressing the cost-effectiveness of insulin analogues compared with human insulin in Sweden, United Kingdom (U.K.), U.S.A, Canada, Switzerland, China, South Korea, Spain, Italy and Poland.

Table 16. Summary of cost-effectiveness analyses for insulin analogues

STUDY/ LOCATION	COMPARISON/MODEL	ICER PER QALY
Valentine, 2011 (Sweden)	• Insulin detemir versus NPH insulin for type 1 diabetes • IMS CORE Diabetes Model	Sweden Health care perspective (SEK 2006) • SEK 49,757 (RM 149,271) Societal perspective • Detemir dominant
Palmer, 2007 (U.K.)	• Insulin detemir plus insulin aspart versus NPH insulin plus human soluble insulin for type 1 diabetes • IMS CORE Diabetes Model	U.K. National Health Service perspective (£ 2004) • £ 2,500 (RM 17,750)
Valentine, 2006 (U.S.A.)	• Insulin detemir plus insulin aspart versus NPH insulin plus human soluble insulin for type 1 diabetes • IMS CORE Diabetes Model	U.S. Health System perspective (USD $ 2005) • USD $ 14,974 (RM 56,901)
Palmer, 2004 (U.K.)	• Insulin detemir only or insulin detemir plus insulin aspart versus NPH insulin only or NPH plus human soluble insulin for type 1 diabetes • IMS CORE Diabetes Model	U.K. National Health Service perspective (£ 2003) • £ 19,285 (RM 129,209)
Cameron, 2009 (Canada)	• IMS CORE Diabetes Model • Insulin aspart versus RHI for type 1 diabetes • Insulin aspart versus RHI for type 2 diabetes • Insulin lispro versus RHI for type 1 diabetes • Insulin lispro versus RHI for type 2 diabetes • Insulin glargine versus NPH for type 1 diabetes • Insulin glargine versus NPH for type 2 diabetes • Insulin detemir versus NPH for type 1 diabetes • Insulin detemir versus NPH for type 2 diabetes	Canadian third-party payer (Can $ 2007) • Cost saving • $ 22,488 (RM 78,708) • $ 28,966 (RM 110,070) • $130,865 (RM 458,027) • $ 87,932 (RM 307,776) • $ 642,994 (RM 2,250,479) • $ 387,729 (RM 1,357,051) • NPH dominant
Brandle, 2011 (Switzerland)	• Insulin glargine versus NPH for type 2 diabetes • Discrete event simulation (DES) model	Switzerland – (CHF 2006) • CHF 26,271 (RM 78,813)
Brandle, 2007 (Switzerland)	• Insulin glargine versus NPH for type 2 diabetes • Diabetes Mellitus Model (DMM)	Switzerland – (CHF 2005) • (Change in HbA1c=-0.12%), ICER = CHF 40,441 to CHF 49,468 (RM 133, 455 to RM 163,244) • (Change in HbA1c=-0.40%), ICER = Glargine dominant to CHF 5,711 (RM 18,846)
Mc Ewan, 2007 (U.K.)	• Insulin glargine versus NPH for type 2 diabetes • Discrete event simulation (DES) model	U.K. National Health Service perspective (£ 2005) • £ 10,027 to £ 13,921 (RM 72,194 to RM 100,231)
Palmer, 2010 (U.S.A)	• BIAsp 30 versus BHI 30 for type 2 diabetes • IMS CORE Diabetes Model	U.S. third party payer perspective (USD $ 2008) • US $ 29,870 (RM 107,532)
Palmer, 2008 (China)	• BIAsp 30 versus BHI 30 for type 2 diabetes • IMS CORE Diabetes Model	China third party payer perspective (CNY 2007) • CNY 1,926 (RM 885)
Lee, 2009 (South Korea)	• BIAsp 30 versus BHI 30 for type 2 diabetes • IMS CORE Diabetes Model	South Korea third party payer perspective (KRW 2007) • KRW 5,915,198 (RM 218,862)
Palmer, 2008 (Sweden, Spain, Italy, Poland)	• Insulin aspart versus human soluble insulin for type 2 diabetes • IMS CORE Diabetes Model	Third party payer perspective • Sweden (€ 2005) and Spain (€ 2006) • Insulin aspart dominant Italy (€ 2006), Poland (€ 2006) • € 18,597 (RM 86,662) € 290,486 (RM 1,353,664)
Pratoomsoot, 2009 (U.K.)	• Insulin lispro versus regular human insulin for type 1 diabetes • IMS CORE Diabetes Model	• U.K. National Health Service perspective (£ 2007) • Lispro dominant

The incremental cost-effectiveness ratio (ICER) based on quality-adjusted life years (QALY) vary across diabetes types and comparisons. Compared with human insulin, insulin detemir was likely to be cost-effective for type 1 diabetes mellitus based on the willingness to pay threshold in Sweden (SEK 100,000 per QALY gained), U.K. (£ 30,000 per QALY gained) and the U.S.A. (USD $ 50,000 per QALY gained).[63-66] Valentine et al. demonstrated that in Sweden, from a healthcare payer perspective the ICER was SEK 49,757 per QALY gained with detemir versus NPH, while detemir was found to be dominant from a societal perspective. The drug costs were higher in the detemir group (SEK 246,569 versus SEK 188,981, difference SEK 57,588) than the conventional human insulin, but this was partly offset by reduced complication costs (SEK 716,544 versus SEK 748,239, difference SEK -31,695). They found that the lifetime indirect costs with detemir treatment were SEK 106,257 lower than with NPH. These savings substantially offset the higher direct costs of SEK 26,144 making insulin detemir a dominant treatment over NPH from a societal perspective.[63] However, in Canada, Cameron et al. demonstrated that at a cost-effectiveness threshold of Can $ 50,000 per quality-adjusted life-year, the probability that each insulin analogues was more cost-effective than conventional insulin was 29.2% for insulin detemir in type 1 diabetes mellitus and 10.8% for insulin detemir in type 2 diabetes mellitus.[67]

Treatment with insulin glargine in type 2 diabetes mellitus may be considered to be cost-effective compared with human insulin based on the willingness to pay threshold in Switzerland (CHF 60,000 per QALY) and in the U.K.[68-70] In contrast, it was not considered to be cost-effective in Canada.[67] Palmer et al. (2010, 2008) and Lee at al. (2000) reported that biphasic insulin aspart 30 could be considered cost-effective compared with biphasic human insulin in treatment of type 2 diabetes mellitus in the U.S.A, China (willingness to pay threshold of CNY 100,000 per QALY gained) and South Korea (willingness to pay threshold of KRW 25 million per QALY gained).[71-73] Insulin aspart would also be considered cost-effective in the treatment of type 2 diabetes mellitus compared with human insulin in Sweden, Spain, Italy and Canada but not in Poland.[74,67] In the U.K., insulin lispro was found to be dominant compared with human insulin in type 1 diabetes mellitus. For the base case scenario, there was a probability of 83.9% that insulin lispro will be cost-effective at a threshold of £30,000 per QALY gained.[75]

Sensitivity analyses were found to change when changes occurred in HbA1c values and hypoglycaemia event rates.[63,67] However, in most studies, variation among any of the key assumptions, including HbA1c did not alter the relative results.[64-66,68-70,72-74] In the sensitivity analysis by Valentine et al. (2011) they found that by assuming there was no benefits when using detemir versus NPH treatment on the rate of major hypoglycaemic events, the ICER increased to SEK 119,711 per QALY gained. Adopting a societal perspective resulted in an ICER of SEK 58,142 per QALY gained for insulin detemir versus NPH.[63] For type 1 diabetes mellitus Cameron et al. demonstrated that when fear of hypoglycaemia was incorporated as a complication in the model, results from sensitivity analyses showed that insulin aspart remained still cost-saving strategy when compared with conventional insulin. However, the ICER per quality-adjusted life year decreased to Can $ 1,117 for insulin lispro, Can $ 17,225 for insulin glargine and Can $ 25,666 for insulin detemir. When no difference in HbA1c between treatment comparators was assumed, ICER increased to Can $ 104,598 for insulin aspart, Can $ 673,041 for insulin lispro, Can $ 916,401 for insulin glargine and Can $ 1,958,928 for insulin detemir.[67]

The costs of severe hypoglycaemia in a population of patients with type 1 diabetes mellitus in the Spanish healthcare system was evaluated by Reviriego et al.[76] They conducted a retrospective study of 100 patients in three Spanish health centres. Resource utilisation data were collected only for interventions specifically relating to the hypoglycaemic episode. The direct medical costs determined in the analyses were; costs of hospitalisation, diagnostic tests carried out, costs of treatment administered and other associated costs such as visits to the endocrinologist and re-training in glucose control, transportation and assistance of a care-giver. In addition, indirect costs such as days of lost of productivity were estimated and, where the clinical records did not include sufficient information for this, the patients were interviewed. The overall mean cost per episode of severe hypoglycaemia was 366 (RM 1,830.00) which comprised of 65.4% direct costs and 34.6% indirect costs. The largest cost was for hospitalisation (183 per episode), which represented 50% of the total costs. They found that the additional cost to prevent one episode of severe hypoglycaemia with insulin lispro over regular human insulin was 277 (RM 1,385.00). The authors concluded that severe hypoglycaemia has a significant impact on the total cost of diabetes. The use of insulin lispro was associated with reductions in annual costs because severe hypoglycaemia and, possibly, the overall effect may be cost neutral or cost saving when total costs were considered. The cost of severe hypoglycaemia should be included in the analysis of total socio-economic burden of diabetes.[76]

7.   DISCUSSION

The scope of our HTA report is broader than other published HTA reports and systematic reviews.[32,34,36,39-41,45-47,51,53,55,60,62] After reviewing the existing published HTA reports and systematic reviews, this review included sixteen more RCTs. Similar to the previous reviews, this review found that there was evidence to suggest treatment with insulin analogues resulted in small but statistically significant reduction in HbA1c level, lower postprandial blood glucose and fasting blood glucose levels. Although, the reduction in HbA1c level was very small, the authors of the UKPDS concluded that any reduction in HbA1c is likely to reduce the risk of complications in type 2 diabetes mellitus.[12] No study designed to investigate the possible long term effects was found.

The risk and fear of hypoglycaemia is a major barrier to effective glycaemic control. Hypoglycaemia is associated with potentially serious and life-threatening outcomes as well as deterioration in the quality of life. There was evidence to suggest that treatment with insulin analogues resulted in lower risk for nocturnal hypoglycaemia and severe hypoglycaemia as reported in certain studies. In contrast with the systematic review by Singh *et al.* we identified a newer systematic review on insulin detemir by Szypowska *et al.* which reported lower overall hypoglycaemia in type 1 diabetes mellitus patients treated with insulin detemir.[33,51 level I] Based on RCTs with accessible patient data, Home *et al.* reported that eight people with type 2 diabetes mellitus needed to be treated with once-daily evening glargine while five people with type 2 diabetes needed to be treated with once-daily morning glargine instead of once-daily evening NPH insulin to avoid one person from experiencing a nocturnal symptomatic hypoglycaemic event within a median of about 25 weeks of starting insulin glargine.[60 level I]

Using the DTSQ, treatment satisfaction was found to be greater in patients treated with insulin analogues, mainly due to changes in the convenience of treatment, flexibility of treatment and satisfaction to continue treatment. This may be associated with the fact that insulin analogues can be administered at mealtimes while conventional human insulin is recommended to be administered roughly 30 minutes prior to eating.[25,36-37,40,44,40-45] Treatment with insulin detemir was also associated with smaller weight gain which is one of the goal of diabetic treatment.[50-53]

The adverse events (excluding hypoglycaemia episodes) were found to be similar in type 1, type 2 diabetes mellitus, gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus treated with insulin analogues compared with conventional human insulin.[32,34,37-38,41-43,45-46,49,52,54,59,62] The foetal and perinatal outcomes were also found to be similar between the two treatment groups.[38,59] The long term safety of insulin glargine compared with NPH insulin was evaluated by Rosenstock *et al.* whereby they reported similar progression in diabetic retinopathy.[61]

Regarding potentially adverse properties such as mitogenic complications or development of carcinogenic effects under insulin analogues, in 2009 the U.S. FDA issued an early communication about safety of insulin glargine to inform the public that U.S. FDA was reviewing four published observational studies, three of which suggested an increased risk of cancer associated with the use of insulin glargine. The U.S. FDA has completed its review of the studies and has determined that the evidence presented in these studies to be inconclusive due to methodological limitations.[77] Similarly, Home PD and Lagarenne P, Colhoun HM, and Chang *et al.* reported that insulin glargine was not associated with an increased risk of cancer.[78-80] Dejgaard *et al.* also reported that patients treated with insulin detemir had a lower or similar occurrence of a cancer diagnosis compared with patients treated with NPH insulin or insulin glargine, respectively.[81]

The prices of insulin analogues vary across countries and regions of the world.[82] Based on modelling for cost-effectiveness analyses, insulin analogues appears to be cost-effective in certain countries.[63-66,68-75] In contrast, Cameron CG, Bennet HA and Waugh *et al.* found that long-acting insulin analogues were not cost-effective for type 2 diabetes mellitus.[67,46]

Model projections indicated that the cumulative incidences of long term complications of diabetes were lower in the insulin analogues group compared with conventional human insulin.[63, 65-69,71-75] Drug costs were higher in the insulin analogues group than the conventional human insulin, but this was partly offset by reduced complication costs.[63,64,68,71-75] All models used different sources of clinical trial data, with some indicated no difference between insulin analogues and human insulin in terms of HbA1c reduction and other using data indicating advantages for insulin analogues. The hypoglycaemia rate and the utility values applied differed across models. These factors likely contribute to the wide range of ICERs, given that HbA1c and hypoglycaemia are the drivers of the models.

Chow *et al.* conducted a cost-analysis of diabetes mellitus treatment and related complications over a five year time horizon in 100 uncontrolled type 2 diabetes mellitus patients treated with NPH insulin versus insulin glargine in Singapore. They demonstrated that patients whose condition were uncontrolled on NPH insulin and continued on NPH insulin, incurred a higher total cost compared if they were switched to insulin glargine. While the treatment cost for the 100 patients continued on NPH was $ 648,457.27 versus $ 891,872.38 after switching to glargine, the consequent lower rate of complications would lead to a reduction in costs of complications ($ 544,508.38 for NPH insulin versus $ 280,494.61 for insulin glargine). Therefore over a period of five years, cost of medical care would be $ 20,598.66 more per 100 patients with uncontrolled type 2 diabetes mellitus continued with NPH insulin.[83]

DiabCare Malaysia 2008, evaluated the current status of diabetes care in Malaysia as a continuation of similar cross-sectional studies conducted previously in 1997, 1998, 2001 and 2003.The study recruited 1,670 patients from general hospitals, diabetes clinics and referral clinics throughout the country from 6 April 2009 to 30 December 2009. They reported the results of type 2 diabetic population who constituted 92.8% of the total population. The study reported deteriorating glycaemic control with mean HbA1c in DiabCare 2008 (8.66 ± 2.09%) which is greater than that of 2003 (7.8% ± 2.2%). In addition, the percentage of patients achieving HbA1c glycaemic targets of < 7.0% was only 22% and the percentage of patients achieving HbA1c glycaemic targets of < 6.5% was only 11.4% compared with 41.0% and 31.2% in 2003, respectively. Microvascular, macrovascular and severe late complications were reported in 75.0%, 28.9% and 25.4% of patients respectively. The rate of diabetic complications were 27.2% for cataract, 7% for microalbuminuria, 45.9% for neuropathy symptoms, 3.8% for leg amputation and 18.4% with history of angina pectoris. The quality of life evaluation showed that about one third of patients have poor quality of life. Insulin prescriptions have almost doubled as compared to 2003; insulin alone (15.4% versus 12.7%), insulin + OADs (38.3% versus 14.4%). The authors concluded that majority of the patients were still not satisfactorily controlled.[84] There are several barriers that may contribute to poor control of diabetes such as non adherence to treatment, adverse events of antidiabetic agents such as hypoglycaemia and weight gain, and poor optimization of therapy including lifestyle and dietary. Therefore, there is a need for intervention which include patient education and the use of newer antidiabetic agents (both oral and insulin) to minimise hypoglycaemia such as the use of insulin analogues as compared to human insulin.

Limitations

Our study has several limitations. In general, the RCTs were limited by the lack of blinding in treatment assignment, the lack of blinding of outcome assessors, patients and care givers. The reason given by the authors for not blinding was differences in the appearance of the basal insulin analogues. Most of the included studies were multicentre and were sponsored by industry. Although models simulate reality but the conclusion made for each economic evaluation is very dependent on the unique data and assumptions made to build up the model. Models are often over simplified and although validated and reputable, the results depend on the assumptions underlying it. Generalizability and international comparisons of economic evaluations are therefore very limited. Although there was no restriction in language during the search but only English full text articles were included in the report.

8. CONCLUSION

8.1. Efficacy or Effectiveness of Insulin Analogues

8.1.1. Rapid-acting insulin analogues

- There was good level of evidence to suggest that treatment with insulin lispro or insulin aspart compared with regular human insulin resulted in small but significantly lower HbA1c values (ranged between 0.09% and 0.14%) in adults with type 1 diabetes mellitus, but not in children.

- The HbA1c values were found to be comparable for the two treatment groups in type 2 diabetes mellitus, gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus. Postprandial blood glucose was also found to be significantly lower in groups treated with insulin lispro or insulin aspart compared with regular human insulin (ranged between 0.83 mmol/L and 1.43 mmol/L). However, fasting and preprandial blood glucose was similar for both treatment groups.

- There was evidence to suggest greater treatment satisfaction in type 1 diabetes mellitus and in pregnant women with type 1 diabetes mellitus treated with insulin lispro or insulin aspart compared with regular human insulin.

- In type 1 and type 2 diabetes mellitus, the HbA1c level was found to be similar between patients treated with insulin glulisine and patients treated with regular human insulin.

8.1.2. Long-acting insulin analogues

- There was good level of evidence to suggest that treatment with insulin glargine compared with NPH insulin resulted in small but significantly lower HbA1c level by 0.11% in adults with type 1 diabetes mellitus but not in children and adolescents or patients with type 2 diabetes mellitus. There was conflicting evidence on the HbA1c values for type 1 diabetes mellitus treated with insulin detemir compared with NPH insulin. For type 2 diabetes mellitus, the HbA1c values were similar in patients treated with insulin detemir compared with NPH insulin. Fasting plasma glucose was found to be significantly lower in type 1 diabetes mellitus treated with insulin glargine or insulin detemir (ranged between 0.87 mmol/L and 1.01 mmol/L), while postprandial blood glucose was found to be significantly lower in type 2 diabetes mellitus treated with insulin glargine compared with NPH insulin.

- In terms of glucose variability, it was found that the mean daily blood glucose (MDBG) and mean amplitude of glucose excursion (MAGE) decreased significantly with insulin glargine but not with NPH insulin in type 1 diabetes mellitus.

- For type 1 and type 2 diabetes mellitus, there was evidence to suggest that quality of life and treatment satisfaction was greater with insulin glargine compared with NPH insulin.

- There was fair to good level of evidence to suggest that treatment with insulin detemir was associated with smaller weight gain in children and adults with type 1 diabetes mellitus and type 2 diabetes mellitus compared with NPH insulin. There was conflicting evidence on body weight changes for patient treated with insulin glargine compared with NPH insulin.

8.1.3. Premixed insulin analogues

- There was good level of evidence to suggest that treatment with premixed insulin analogues had similar effect in lowering HbA1c but significantly reduced postprandial blood glucose in type 1 and type 2 diabetes mellitus [ranged between 17.8 mg/dL (0.98 mmol/L) and 30.3 mg/dL (1.68 mmol/L)] compared with premixed human insulin.

8.2. Safety

8.2.1. Rapid-acting insulin analogues

- There was good level of evidence to suggest that when compared with regular human insulin, the use of insulin lispro resulted in lower risk for nocturnal hypoglycaemia in adults and adolescents with type 1 diabetes mellitus (reduction by 49% and 39% respectively) and also in type 2 diabetes mellitus in some studies.

- The risk for severe hypoglycaemia was also lower in adult with type 1 diabetes mellitus by 20%.

- Similarly, treatment with insulin aspart resulted in lower risk for nocturnal hypoglycaemia (reduction between 33% and 45%) in type 1 diabetes mellitus. However, there were no differences in the risk for overall hypoglycaemia in patients treated with insulin lispro or insulin aspart compared with regular human insulin.

- There was fair level of evidence to suggest that the rate of major maternal or major nocturnal maternal hypoglycaemia and foetal or perinatal outcomes was similar in gestational diabetes mellitus and pregnant women with type 1 diabetes mellitus treated with insulin aspart compared with regular human insulin.

- There was limited good level of evidence to suggest that compared with regular human insulin, treatment with insulin glulisine resulted in similar risk for overall, severe and nocturnal hypoglycaemia.

- There was good level of evidence to suggest that the frequency and type of adverse events (other than hypoglycaemia) were similar between rapid-acting insulin analogues and regular human insulin. Most of the events were mild in severity such as respiratory tract infections, headaches, flu symptoms, pain and injection site reactions and were not considered to be related to one of the treatments.

8.2.2. Long-acting insulin analogues

- There was good level of evidence to suggest that there were similar risk for overall, severe and nocturnal hypoglycaemia for type 1 diabetes mellitus treated with insulin glargine compared with NPH insulin.

- In patients with type 2 diabetes mellitus, the risk for nocturnal and overall hypoglycaemia was significantly lower in patients treated with insulin glargine compared with NPH insulin by 34% to 46% and 11% respectively. Five people with type 2 diabetes mellitus needed to use once daily morning glargine rather than once-daily evening NPH, while eight people with type 2 diabetes needed to use once-daily evening glargine rather than once-daily evening NPH to avoid one person from experiencing a nocturnal symptomatic hypoglycaemic event.

- There was good level of evidence to suggest that treatment with insulin detemir compared with NPH insulin resulted in lower risk for nocturnal hypoglycaemia in type 1 diabetes mellitus (adult, children and adolescents) by 8% to 15%, while severe hypoglycaemia was found to be lower in adult with type 1 diabetes mellitus by 25% to 34%.

- Type 2 diabetes mellitus treated with insulin detemir was found to have significantly lower risk for nocturnal and overall hypoglycaemia (reduction by 34% to 47% and 18% to 32%, respectively).

- There was good level of evidence to suggest similar foetal and neonatal outcomes for patients with gestational diabetes mellitus or pregnant women with type 1 diabetes mellitus treated with insulin glargine compared with NPH insulin.

- The was fair level of evidence to suggest that the progression of diabetic retinopathy was similar in type 2 diabetes mellitus patients treated with insulin glargine compared with NPH insulin.

8.2.3. Premixed insulin analogues

• There was good level of evidence to suggest that the risk for hypoglycaemia was similar for premixed insulin analogues and premixed human insulin.

8.3. Cost / cost-effectiveness / economic evaluation

• Based on modelling for cost-effectiveness analyses and also the willingness to pay threshold of each country, insulin detemir could be considered be cost-effective in Sweden, U.K. and the U.S.A. but not in Canada. Similarly, insulin glargine could be considered cost-effective in Switzerland and U.K. but not in Canada. BiAsp 30 could be considered cost-effective in U.S.A., China and South Korea while insulin Aspart could be considered cost-effective in Canada, Sweden, Spain and Italy but not Poland. Insulin lispro was found to be dominant in the U.K. and was associated with reductions in annual costs of diabetes in Spain by reducing the frequency of severe hypoglycaemia. The drug costs were higher in the insulin analogues group than the conventional human insulin, but this was partly offset by reduced complication costs.

9. RECOMMENDATION

Based on the above review, treatment with insulin analogues compared with conventional human insulin appeared to offer minor benefit in terms of glycaemic control as reflected in HbA1c level, postprandial blood glucose and fasting blood glucose but have advantages in terms of reduced occurrence of hypoglycaemia, particularly nocturnal hypoglycaemia and severe hypoglycaemia as reported in some studies. While the adverse events (excluding hypoglycaemia episodes) were found to be similar in both treatment groups, patients treated with insulin analogues showed greater treatment satisfaction and less weight gain. Hence, it is recommended that insulin analogues should be made available for treatment of all type 1 diabetes mellitus and for type 2 diabetes mellitus who have recurrent hypoglycaemia. However, it is not recommended for gestational diabetes mellitus. More high quality clinical trials are warranted to provide evidence on long term safety and effectiveness of insulin analogues. Although insulin analogues could be considered cost-effective in some countries, generalizability and international comparisons of economic evaluations are limited. Local cost analyses research with the decision maker and societal perspective are encouraged. The price of insulin analogues in Malaysia is much higher compared with conventional human insulin. From literature review, we observed that there were price variations across countries and regions of the world. Hence, we need to negotiate for better pricing package.

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11. APPENDICIES

APPENDIX 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

Designation of levels of evidence

I   Evidence obtained from at least one properly designed randomized controlled trial.

II-I   Evidence obtained from well-designed controlled trials without randomization.

II-2   Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3   Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III   Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL INSULIN ANALOGUES

1. BACKGROUND INFORMATION

Diabetes mellitus still remains one of the most significant causes of morbidity and mortality in the world, and its global impact is likely to accelerate over the coming decades. According to the World Health Organization (WHO), 346 million people worldwide have diabetes and more than 80% of diabetes deaths occur in low-and middle income countries. The WHO projects that diabetes deaths will double between 2005 and 2030. The global health expenditure on diabetes is expected to total at least United States Dollars (USD) 376 billion or International Dollars (ID) 418 billion in 2010 and USD 490 billion or ID 561 billion in 2030.[2] The WHO defines diabetes mellitus as "a metabolic disorder of multiple aetiology characterised by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both". There are two main types of diabetes: Type 1 diabetes usually develops in childhood and adolescence and patients require lifelong insulin injections for survival. Type 2 diabetes usually develops in adulthood and is related to obesity, lack of physical activity, and unhealthy diets. This is the more common type of diabetes (representing 90% of diabetic cases worldwide) and treatment may involve lifestyle changes and weight loss alone, or oral medications or even insulin injections. Other categories of diabetes include gestational diabetes (a state of hyperglycaemia which develops during pregnancy) and other rare causes (genetic syndromes, acquired processes such as pancreatitis, diseases such as cystic fibrosis, exposure to certain drugs, viruses, and unknown causes).[3]

In the short term, hyperglycaemia causes symptoms of increased thirst, increased urination, increased hunger, and weight loss. However, in the long-term, it causes microvascular and macrovascular complications. Microvascular complications include diabetic retinopathy leading to blindness, nephropathy leading to renal failure, neuropathy leading to impotence and diabetic foot disorders. Macrovascular complications include cardiovascular diseases such as heart attacks, strokes and insufficiency in blood flow to the legs. In addition, the risk of tuberculosis is three times higher among people with diabetes.

According to the WHO global status report on non communicable diseases 2010, the global prevalence of diabetes in 2008 was estimated to be 10% in adults aged 25 years and above. The prevalence of diabetes was highest in the Eastern Mediterranean Region and the Region of the Americas (11% for both sexes) and lowest in the WHO European and Western Pacific Regions (9% for both sexes).[7] According to the Malaysian National Health Morbidity Survey III, in 2006 the overall prevalence of diabetes mellitus was 11.6%. The Indians had the highest prevalence of 19.9%, followed by Malays 11.9% and Chinese 11.4%. It was reported that 4.3% of patients with known diabetes had amputation, 3.4% had suffered a stroke event and 1.6% was on some form of renal replacement therapy. Usage of insulin alone or in combinations was low at 7.2% of patients. Zhang *et al.* reported that the health expenditure for diabetes among adults aged 20 to 79 years for 2010 in Malaysia was estimated between USD 600,407.75 and USD 1,005,095.05 (16% of the health expenditure). It is estimated that in 2030, the health expenditure for diabetes will increase to between USD 1,073,139.00 and USD 1,828,693.40.

Two clinical studies, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) published in 1993, 1998 and 2008 have demonstrated that intensive control of serum glucose levels can minimize the development of diabetes-related complications. Malaysian Ministry of Health Clinical Practice Guidelines on Management of Type 2 Diabetes Mellitus (4th Edition) 2009, recommended that therapy for most patients with type 2 diabetes mellitus should be targeted to achieve a HbAlc of less than 6.5%. Thus the primary goal of treatment is to bring the elevated blood sugars down to a normal range. Therefore, physicians and patients should strive to mimic, as closely as possible, the serum level of insulin produced in a healthy person. Success with insulin management ultimately depends on how closely a given regimen can mimic normal physiologic insulin release patterns. Human insulin (conventional insulin) is synthetic insulin which is laboratory created by growing insulin proteins within Escherichia coli to mimic the insulin in humans. It is available in two forms: a short acting (regular) form and an intermediate acting [Neutral Protamine Hagedorn (NPH)] form.

While management of diabetes has greatly improved in recent years with newer strategies focusing on aggressive glucose control, it is claimed that the conventional insulin products have fallen short of providing optimal therapy. The new insulin analogues (IA) including rapid-acting insulin analogues, the long-acting basal insulin analogues and premixed insulin analogues formulations have been designed to more closely mimic physiologic insulin profiles through improved pharmacokinetic characteristics, which result in either more rapid or prolonged pharmacodynamic effects. Rapid-acting also known as short-acting insulin analogues are designed to offer a more rapid onset of action and shorter duration of activity than regular human insulin. Currently, there are three commercially available rapid-acting insulin analogues: insulin aspart, insulin lispro and insulin glulisine. It can be administered at mealtimes and produce a rapid and short-lived insulin spike to address postprandial glucose elevations. This imparts a significant advantage in convenience for patients relative to human insulin, which is recommended to be administered roughly 30 minutes prior to eating. There are currently two long-acting basal insulin analogues preparations available: insulin glargine and insulin detemir which have been designed to approach the ideal characteristics of basal insulin by having a relatively flat, 24-hour basal insulin supply, with less variability in action compared to human NPH insulin. Three types of fixed-ratio insulin analogues mixes are currently available: a 75% insulin lispro protamine suspension with 25% insulin lispro, a 50% insulin lispro protamine suspension with 50% insulin lispro, a 70% insulin aspart protamine suspension with 30% insulin aspart. These formulations have been developed to minimise the errors that can occur when patients self-mix insulin combinations.

Despite these clear pharmacologic advantages, measurable clinical benefits in a complex disease such as diabetes can be hard to measure. Several systematic reviews and health technology assessment (HTA) have evaluated the clinical efficacy of insulin analogues, however there were uncertainty regarding their optimal use or its long term efficacy and safety. In some Asian countries such as Korea, Taiwan, Philippines and in many developed countries, insulin analogues have completely replaced the use of conventional insulin both in outpatient and inpatient management of diabetes mellitus. In Malaysia, the use of insulin analogues in public hospitals range from 2% to 3%. This is because insulin analogues are more expensive (three to five times) than conventional insulin. Because health care resources are limited, there is a need to determine if insulin analogues are justified for all or some diabetic groups. This HTA was requested by the Head of Endocrinology Services, Ministry of Health.

2.   POLICY QUESTION

In Ministry of Health facilities, should insulin analogues be used for all diabetic patients treated with insulin?

Research questions

i.   How safe is rapid-acting (short-acting) insulin analogues, premixed insulin analogues or long-acting insulin analogues compared with conventional insulin in treatment of type 1, type 2, or gestational diabetes mellitus?

ii.   What are the short and long term benefits of using rapid-acting (short-acting) insulin analogues, premixed insulin analogues or long-acting insulin analogues compared with conventional insulin in treatment of type 1, type 2, or gestational diabetes mellitus?

iii.   What are the economic implications of using insulin analogues in the treatment of type 1, type 2, or gestational diabetes mellitus?

3.   OBJECTIVE

3.1.   To assess the safety and efficacy of rapid-acting (short-acting) insulin analogues, premixed insulin analogues or long-acting insulin analogues compared with conventional insulin in treatment of type 1, type 2, or gestational diabetes mellitus.

3.2.   To assess the economic implications of using insulin analogues in treatment of type 1, type 2, or gestational diabetes mellitus.

4. METHODOLOGY

4.1 Search Strategy

4.1.1   Electronic database will be searched for published literatures pertaining to the use of insulin analogues in treatment of type 1, type 2, or gestational diabetes mellitus.

4.1.2   Databases as follows: MEDLINE, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-DARE and EBM Reviews-NHS Economic Evaluation Database through the Ovid interface. Searches will also be conducted in PubMed, Horizon Scanning database, INAHTA database, and FDA database.

4.1.3   Additional literatures will be identified from the references of the retrieved articles.

4.1.4   General search engine will also be used to get additional web-based materials and information.

4.1.5   Limit search for RCT from 2006 onwards.

4.1.6   The detail of the search strategy will be presented as appendix.

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

a. Study design	:	HTA report, Systematic Review, Randomised Controlled Trials (RCT) and studies which include economic evaluation.
b. Population	:	Patients with diabetes mellitus (type 1, type 2, or gestational diabetes mellitus).
c. Intervention	: i.	Rapid-acting (short-acting) insulin analogues: (insulin lispro or insulin aspart or insulin glulisine).
	ii.	Long-acting insulin analogues (insulin glargine or insulin detemir).
	iii.	Premixed insulin analogues (insulin 75% neutral protamine, 25% lispro or 50% neutral protamine, 50% lispro or 70% protamine aspart, 30% aspart).
d. Comparators	: i.	Regular human insulin.
	ii.	Neutral Protamine Hagedorn (NPH insulin).
	iii.	Premixed insulin preparations (NPH/regular 70/30, NPH/ regular 50/50).
	iv.	Combination of human insulin with oral anti-diabetic agents (OADs) or IA.
e. Outcome	: i.	Glycaemic control - glycosylated haemoglobin (HbA1c), fasting plasma glucose, 24 hour glucose profile, glucose variability.
	ii.	Hypoglycaemic episodes (overall number, severe episodes, nocturnal hypoglycaemia episodes and neonatal hypoglycaemia).
	iii.	Quality of life assessment.
	iv.	Adverse events or complications related to the use of insulin analogues (for example local reaction, carcinogenicity, teratogenicity, and sudden intrauterine demise among gestational diabetes).
	v.	Diabetic complications (nephropathy, retinopathy, neuropathy, and other diabetes related complications).
	vi.	Mortality (total and diabetes related mortality).
	vii.	Weight changes.
	viii.	Costs.
f. Treatment duration:		Four weeks and above
g. Full text articles published in English		

4.2.2 Exclusion criteria

a. Study design: Animal study, labaratory study, narrative review, cross-sectional study, cohort and case-control studies.

b. Non English full text article.

c. Studies which compare insulin analogue with another insulin analogue.

Based on the above inclusion and exclusion criteria, study selection will be carried out independentlyby two reviewers. Disagreement will be resolved by discussion.

4.3 Data extraction strategy

The following data will be extracted:

4.3.1 Details of methods and study population characteristics.

4.3.2 Details of intervention and comparators.

4.3.3 Details of individual outcomes for safety, efficacy and cost evaluation associated with the use of insulin analogues.

Data will be extracted from selected studies by two reviewers using a pre-designed data extraction form. Disagreements will be resolved by discussion.

4.4 Quality assessment strategy

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Critical Appraisal Skill Programme (CASP) by two reviewers depending on the type of the study design or (Jadad score for RCT).

4.5 Methods of analysis/synthesis

Data on the safety, efficacy and cost implication of using insulin analogues in treatment of type 1, type 2, or gestational diabetes mellitus will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment.

5. REPORT WRITING

SEARCH STRATEGY

Ovid MEDLINE® In-process & other Non-Indexed citations and Ovid MEDLINE® 1948 to present

1. Diabetes Mellitus/
2. Diabetes mellitus.tw.
3. Glucose intolerance.tw.
4. Diabetes Mellitus, Type 1/
5. (autoimmune adj1 diabetes).tw.
6. Iddm.tw.
7. ((insulin-dependent or insulin dependent or ketosis-prone or ketosis prone or juvenile-onset or juvenile onset or type 1 or type I or type I or sudden-onset or sudden onset) adj1 diabetes mellitus).tw.
8. Diabetes Mellitus, Type 2/
9. mody.tw.
10. niddm.tw.
11. ((type 2 or type ii or type II or non-insulin-dependent or non insulin dependent or adult-onset or adult onset or maturity- onset or maturity onset or slow- onset or slow onset or ketosis-resistant or ketosis resistant) adj1 diabetes mellitus).tw.
12. Diabetes, Gestational/
13. (gestational adj1 (diabetes or diabetes mellitus)).tw.
14. ((pregnancy- induced or pregnancy induced) adj1 diabetes).tw.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. (insulin adj1 analog$).tw.
17. novo nordisk brand of insulin.tw.
18. aspart.tw.
19. novorapid.tw.
20. novolog.tw.
21. (insulin adj1 b28 asp).tw.
22. b28-asp-insulin.tw.
23. (insulin adj1 aspart).tw.
24. Insulin-aspart.tw.
25. (insulin adj (lispro or glulisine)).tw.
26. lispro.tw.
27. humalog.tw.
28. glulisine.tw.
29. Apida.tw.
30. (insulin adj (determir or glargine)).tw.
31. determir.tw.
32. levemir.tw.
33. glargine.tw.
34. Lantus.tw.
35. Insulin Aspart/
36. (premixed adj (insulin analog$ or analog$ insulin)).tw.
37. Insulin Lispro/
38. Humalog mix 25.tw.
39. 50% neutral protamine lispro, 50% lispro.tw.
40. 75% neutral protamine lispro, 25% lispro.tw.
41. Humalog Mix 50.tw.
42. 70% neutral protamine aspart, 30% aspart.tw.
43. NovoMix 30.tw.
44. ((rapid-acting or rapid acting or short-acting or short acting or long-acting or long acting or postprandial or basal) adj insulin analog$).tw.
45. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. Insulin/
47. (insulin adj1 (b chain or a chain or soluble or regular or sodium or semilente or long acting or long-acting or nph or isophane or protamine zinc or regular isophane or protamine hagedorn or neutral protamine hagedorn)).tw.
48. Iletin.tw.
49. Actrapid.tw.
50. zinc insulin protamine.tw.
51. hagedorn insulin protamine.tw.
52. Insulatard.tw.

53. ((regular or short-acting or short acting or synthetic or long- acting or long acting or lente or ultralente or intermediate-acting or intermediate acting or premixed) adj human insulin).tw.

54. (humulin adj (S or R or N or I or L or M2 or M3 or M5)).tw.

55. (Novolin adj (R or N or L)).tw.

56. (Insuman adj (rapid or basal or Comb)).tw.

57. Mixtard.tw.

58. 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57

59. 15 and 45 and 58

Ovid- EBM Reviews- Cochrane Central Register of Controlled Trials (March 2012)

1. Diabetes Mellitus/

2. Diabetes mellitus.tw.

3. Glucose intolerance.tw.

4. Diabetes Mellitus, Type 1/

5. (autoimmune adj1 diabetes).tw.

6. Iddm.tw.

7. ((insulin-dependent or insulin dependent or ketosis-prone or ketosis prone or juvenile-onset or juvenile onset or type 1 or type I or type l or sudden-onset or sudden onset) adj1 diabetes mellitus).tw.

8. Diabetes Mellitus, Type 2/

9. mody.tw.

10. niddm.tw.

11. ((type 2 or type ii or type II or non-insulin-dependent or non insulin dependent or adult-onset or adult onset or maturity- onset or maturity onset or slow- onset or slow onset or ketosis-resistant or ketosis resistant) adj1 diabetes mellitus).tw.

12. Diabetes, Gestational/

13. (gestational adj1 (diabetes or diabetes mellitus)).tw.

14. ((pregnancy- induced or pregnancy induced) adj1 diabetes).tw.

15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16. (insulin adj1 analog$).tw.

17. novo nordisk brand of insulin.tw.

18. aspart.tw.

19. novorapid.tw.

20. novolog.tw.

21. (insulin adj1 b28 asp).tw.

22. b28-asp-insulin.tw.

23. (insulin adj1 aspart).tw.

24. Insulin-aspart.tw.

25. (insulin adj (lispro or glulisine)).tw.

26. lispro.tw.

27. humalog.tw.

28. glulisine.tw.

29. Apida.tw.

30. (insulin adj (determir or glargine)).tw.

31. determir.tw.

32. levemir.tw.

33. glargine.tw.

34. Lantus.tw.

35. Insulin Aspart/

36. (premixed adj (insulin analog$ or analog$ insulin)).tw.

37. Insulin Lispro/

38. Humalog mix 25.tw.

39. 50% neutral protamine lispro, 50% lispro.tw.

40. 75% neutral protamine lispro, 25% lispro.tw.

41. Humalog Mix 50.tw.

42. 70% neutral protamine aspart, 30% aspart.tw.

43. NovoMix 30.tw.

44. ((rapid-acting or rapid acting or short-acting or short acting or long-acting or long acting or postprandial or basal) adj insulin analog$).tw.

45. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46. Insulin/

47. (insulin adj1 (b chain or a chain or soluble or regular or sodium or semilente or long acting or long-acting or nph or isophane or protamine zinc or regular isophane or protamine hagedorn or neutral protamine hagedorn)).tw.

48. Iletin.tw.

49. Actrapid.tw.

50. zinc insulin protamine.tw.
51. hagedorn insulin protamine.tw.
52. Insulatard.tw.
53. ((regular or short-acting or short acting or synthetic or long- acting or long acting or lente or ultralente or intermediate-acting or intermediate acting or premixed) adj human insulin).tw.
54. (humulin adj (S or R or N or I or L or M2 or M3 or M5)).tw.
55. (Novolin adj (R or N or L)).tw.
56. (Insuman adj (rapid or basal or Comb)).tw.
57. Mixtard.tw.
58. 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59. 15 and 45 and 58
60. limit 59 to yr="2006 -Current"

Ovid- EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2012)

1. Diabetes Mellitus/
2. Diabetes mellitus.tw.
3. Glucose intolerance.tw.
4. Diabetes Mellitus, Type 1/
5. (autoimmune adj1 diabetes).tw.
6. Iddm.tw.
7. ((insulin-dependent or insulin dependent or ketosis-prone or ketosis prone or juvenile-onset or juvenile onset or type 1 or type I or type l or sudden-onset or sudden onset) adj1 diabetes mellitus).tw.
8. Diabetes Mellitus, Type 2/
9. mody.tw.
10. niddm.tw.
11. ((type 2 or type ii or type II or non-insulin-dependent or non insulin dependent or adult-onset or adult onset or maturity- onset or maturity onset or slow- onset or slow onset or ketosis-resistant or ketosis resistant) adj1 diabetes mellitus).tw.
12. Diabetes, Gestational/
13. (gestational adj1 (diabetes or diabetes mellitus)).tw.
14. ((pregnancy- induced or pregnancy induced) adj1 diabetes).tw.
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. (insulin adj1 analog$).tw.
17. novo nordisk brand of insulin.tw.
18. aspart.tw.
19. novorapid.tw.
20. novolog.tw.
21. (insulin adj1 b28 asp).tw.
22. b28-asp-insulin.tw.
23. (insulin adj1 aspart).tw.
24. Insulin-aspart.tw.
25. (insulin adj (lispro or glulisine)).tw.
26. lispro.tw.
27. humalog.tw.
28. glulisine.tw.
29. Apida.tw.
30. (insulin adj (determir or glargine)).tw.
31. determir.tw.
32. levemir.tw.
33. glargine.tw.
34. Lantus.tw.
35. Insulin Aspart/
36. (premixed adj (insulin analog$ or analog$ insulin)).tw.
37. Insulin Lispro/
38. Humalog mix 25.tw.
39. 50% neutral protamine lispro, 50% lispro.tw.
40. 75% neutral protamine lispro, 25% lispro.tw.
41. Humalog Mix 50.tw.
42. 70% neutral protamine aspart, 30% aspart.tw.
43. NovoMix 30.tw.
44. ((rapid-acting or rapid acting or short-acting or short acting or long-acting or long acting or postprandial or basal) adj insulin analog$).tw.
45. 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46. 15 and 45

Pubmed Search terms

((((((((("diabetes mellitus"[MeSH Terms]) OR "diabetes mellitus"[Title/Abstract]) OR "Glucose intolerance"[Title/Abstract]) OR ((("diabetes mellitus, type 1"[MeSH Terms]) OR Diabetes, Autoimmune AND "[Title/Abstract]) OR " AND Autoimmune Diabetes AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Sudden-Onset AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Sudden Onset AND "[Title/Abstract]) OR " AND Sudden-Onset Diabetes Mellitus AND "[Title/Abstract]) OR " AND Sudden Onset, Diabetes Mellitus AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Insulin-Dependent AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Insulin Dependent AND "[Title/Abstract]) OR " AND Insulin-Dependent Diabetes Mellitus AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Ketosis-Prone AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Ketosis Prone AND "[Title/Abstract]) OR " AND Ketosis-Prone Diabetes Mellitus AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Ketosis-Resistant AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Ketosis Resistant AND "[Title/Abstract]) OR " AND Ketosis-Resistant Diabetes Mellitus AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Juvenile-Onset AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Juvenile Onset AND "[Title/Abstract]) OR " AND Juvenile-Onset Diabetes Mellitus AND "[Title/Abstract]) OR " AND Type 1 Diabetes Mellitus AND "[Title/Abstract]) OR " AND Diabetes Mellitus, Type I[Title/Abstract]) OR IDDM[Title/Abstract])) OR ((((((((((((((((("diabetes mellitus, type 2"[MeSH Terms]) OR "Diabetes Mellitus, Maturity-Onset"[Title/Abstract]) OR "Diabetes Mellitus, Maturity Onset"[Title/Abstract]) OR "Maturity-Onset Diabetes Mellitus"[Title/Abstract]) OR "Maturity Onset Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Adult-Onset"[Title/Abstract]) OR "Adult-Onset Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Adult Onset"[Title/Abstract]) OR "Diabetes Mellitus, Non Insulin Dependent"[Title/Abstract]) OR "Diabetes Mellitus, Non-Insulin-Dependent"[Title/Abstract]) OR "Non-Insulin-Dependent Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Noninsulin Dependent"[Title/Abstract]) OR "Type 2 Diabetes Mellitus"[Title/Abstract]) OR "Diabetes Mellitus, Type II"[Title/Abstract]) OR "Diabetes Mellitus, Slow-Onset"[Title/Abstract]) OR "Diabetes Mellitus, Slow Onset"[Title/Abstract]) OR "Slow-Onset Diabetes Mellitus"[Title/Abstract]) OR MODY[Title/Abstract]) OR NIDDM[Title/Abstract])) OR (((((((("diabetes, gestational"[MeSH Terms]) OR "Diabetes, Pregnancy-Induced"[Title/Abstract]) OR "Diabetes, Pregnancy Induced"[Title/Abstract]) OR "Pregnancy-Induced Diabetes"[Title/Abstract]) OR "Gestational Diabetes"[Title/Abstract]) OR "Diabetes Mellitus, Gestational"[Title/Abstract]) OR "Gestational Diabetes Mellitus"[Title/Abstract]))) AND ((((((((((((((((Insulin*[MeSH Terms]) OR "Insulin, Regular"[Title/Abstract]) OR "Regular Insulin"[Title/Abstract]) OR "Soluble Insulin"[Title/Abstract]) OR "Insulin, Soluble"[Title/Abstract]) OR "Insulin A Chain"[Title/Abstract]) OR "Sodium Insulin"[Title/Abstract]) OR "Insulin, Sodium"[Title/Abstract]) OR Novolin[Title/Abstract]) OR Iletin[Title/Abstract]) OR "Insulin B Chain"[Title/Abstract]) OR "Chain, Insulin B"[Title/Abstract])) OR (((("Insulin, regular, human"[MeSH Terms]) OR "Humulin S"[Title/Abstract]) OR "Humulin R"[Title/Abstract]) OR "Novolin R"[Title/Abstract])) OR ((((((("Insulin, short-acting"[MeSH Terms]) OR "Insulin, Short Acting"[Title/Abstract]) OR "Short-Acting Insulin"[Title/Abstract]) OR "Insulin, Rapid-Acting"[Title/Abstract]) OR "Insulin, Rapid Acting"[Title/Abstract]) OR "Rapid-Acting Insulin"[Title/Abstract])) OR ((("Insulin, long-acting"[MeSH Terms]) OR Insulin, long- acting AND "[Title/Abstract]) OR " AND Insulin, Long acting AND "[Title/Abstract]) OR " AND Long-Acting Insulin AND "[Title/Abstract]) OR " AND Long Acting Insulin AND "[Title/Abstract]) OR Insulin, Semilente[Title/Abstract]) OR "Semilente Insulin"[Title/Abstract])) OR (((((("Insulin, long-acting, human"[MeSH Terms]) OR "insulin, protamine zinc, human"[Title/Abstract]) OR "insulin, ultralente, human"[Title/Abstract]) OR "insulin, lente, human"[Title/Abstract]) OR "Insulin, Monotard"[Title/Abstract]) OR "Monotard Insulin"[Title/Abstract])) OR (((((((((((("Insulin, isophane"[MeSH Terms]) OR "Intermediate-acting insulin"[Title/Abstract]) OR "intermediate acting insulin"[Title/Abstract]) OR "Isophane Insulin"[Title/Abstract]) OR "Isophane Insulin, Regular"[Title/Abstract]) OR "Regular Isophane Insulin"[Title/Abstract]) OR "NPH Insulin"[Title/Abstract]) OR "Insulin, NPH"[Title/Abstract]) OR "Protamine Hagedorn Insulin"[Title/Abstract]) OR "Hagedorn Insulin, Protamine"[Title/Abstract]) OR "Neutral Protamine Hagedorn Insulin"[Title/Abstract]) OR "Insulin, Protamine Zinc"[Title/Abstract]) OR "Protamine Zinc Insulin"[Title/Abstract]) OR "Zinc Insulin, Protamine"[Title/Abstract])) OR ((((((((("Premixed human insulin"[Title/Abstract]) OR "Humulin M2"[Title/Abstract]) OR "Humulin M3"[Title/Abstract]) OR "Humulin M5"[Title/Abstract]) OR "Novolin 70/30"[Title/Abstract]) OR "Humulin 70/30"[Title/Abstract]) OR "Humulin 50/50"[Title/Abstract]) OR "Insuman Comb"[Title/Abstract]) OR "Mixtard 70/30"[Title/Abstract]))) AND ((((((((("Insulin analog*"[Title/Abstract]) OR "Analog* insulin"[Title/Abstract]) OR "Rapid acting insulin analog*"[Title/Abstract]) OR "rapid-acting insulin analog*"[Title/Abstract])) OR ((((((((("insulin aspart"[MeSH Terms]) OR "Aspart, Insulin"[Title/Abstract]) OR "Insulin-Aspart"[Title/Abstract]) OR "Insulin B28asp"[Title/Abstract]) OR "B28asp, Insulin"[Title/Abstract]) OR "B28-Asp-Insulin"[Title/Abstract]) OR "B28 Asp Insulin"[Title/Abstract]) OR "Insulin, Aspartic Acid(B28)-"[Title/Abstract]) OR NovoLog[Title/Abstract]) OR NovoRapid[Title/Abstract]) OR "Novo Nordisk Brand of Insulin Aspart"[Title/Abstract])) OR (("short acting insulin analog*"[Title/Abstract]) AND "short-acting insulin analog*"[Title/Abstract])) OR (((((((((((insulin lispro[MeSH Terms]) OR "Lispro, Insulin"[Title/Abstract]) OR "28(B)-Lysine-29(B)-Prolineinsulin"[Title/Abstract]) OR LYSPRO[Title/Abstract]) OR "Insulin, Lysyl(28B)-Prolyl(28B)-"[Title/Abstract]) OR Lispro[Title/Abstract]) OR "28(B)-Lys-29(B)-Pro-Insulin"[Title/Abstract]) OR "Insulin, Lys(28B)-Pro(29B)-"[Title/Abstract]) OR "Humalog"[Title/Abstract]) OR "Eli Lilly brand of Insulin Lispro"[Title/Abstract]) OR "Insulin Glulisine"[Title/Abstract]) OR Apida[Title/Abstract])) OR ((((((((("Long acting insulin analog*"[Title/Abstract]) OR "long-acting insulin analog*"[Title/Abstract]) OR "Postprandial insulin anlog*"[Title/Abstract]) OR "Basal insulin analog*"[Title/Abstract]) OR "Insulin detemir"[Title/Abstract]) OR Levemir[Title/Abstract]) OR "basal insulin detemir"[Title/Abstract]) OR "Insuline glargine "[Title/Abstract]) OR Lantus[Title/Abstract])) OR (((((((((((((Premixed insulin analog*[Title/Abstract]) OR premixed analog* AND insulin[Title/Abstract]) OR "premixed insulin"[Title/Abstract]) OR "75% neutral protamine lispro, 25% lispro"[Title/Abstract]) OR "75/25 humalog"[Title/Abstract]) OR "Humalog Mix 25"[Title/Abstract]) OR "Lilly brand of insulin lispro, isophane insulin lispro drug combination (25:75)"[Title/Abstract]) OR "50% neutral protamine lispro, 50% lispro"[Title/Abstract]) OR "50/50 humalog"[Title/Abstract]) OR "Humalog mix 50"[Title/Abstract]) OR "70% neutral protamine aspart, 30% aspart"[Title/Abstract]) OR "70/30 Movolog"[Title/Abstract]) OR "NovoMix 30"[Title/Abstract]))

Evidence Table	: Effectiveness
Question	: Is short-acting insulin analogues effective for treatment of diabetes mellitus compared to conventional human insulin?

Bibliographic citation	1. Barnajee S, Tran K, Li H, Cimon K, Daneman D, Simpson S, Campbell K. Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness. Technology report No 87. Ottawa: Canadian Agency for drugs and Technologies in Health, 2007.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to evaluate the clinical and economic implications of short-acting insulin analogues [insulin Lispro (ILis), insulin aspart (IAsp), and insulin glulisine (IGlu)] for the treatment of type 1, type 2, and gestational diabetes mellitus (DM). Electronic searches of the MEDLINE, BIOSIS Previews, PASCAL and EMBASE databases were searched from 1990 until January 2006 with no language restrictions. Parallel search was run on PubMed and Cochrane databases. Last Cochrane updates were performed on February 6, 2006. Grey literature was also searched. Two reviewers independently selected trials for inclusion. Data from each included trial were extracted by two of three individuals working independently and using a structured form. The quality of the included RCTs was evaluated using the Jadad five-point scale. Cochrane software Review Manager 4.2.3 was used to analyse data and generate forest plots. If I^2 >75% the studies were not pooled. A review of economic studies and budget impact analysis were performed
LE	I
Number of patients & Patient characteristics	A total of 86 RCTs were included:- • 47 on type 1 DM • 26 on type 2 DM • 10 on Type 1 and 2 combined • 3 on gestational DM Most of the studies were of low methodological quality (Jaded score ≤ 2) RCTs on type 1 DM:- • Number of patients in the trials varied between 10 and 1,070 • 8 involved paediatric population (mean age ranged between 8 and 15 years) • 39 involved mainly adults (mean age ranged 23 to 48 years) • 29 cross over trials and 18 parallel trials • 31 mentioned industry sponsorship RCTs on type 2 DM:- • Number of patients in the trials varied between 21 and 876 • 25 reported mean age (between 54 and 68 years) • 7 cross over trials and 20 parallel trials • 19 mentioned industry sponsorship RCTs on type 1 and type 2 DM • Mean age ranged between 32 and 64 years • Number of females varied between 28% to 59% RCTs on gestational DM • 2 journal articles and one conference abstract • 1 mentioned industry sponsorship • All compared ILis with HI • Two reported mean age ranging between 30 and 35 years
Intervention	Short-acting insulin analogues (ILis, IAsp, or IGlu)
Comparison	Conventional human insulin (HI) or oral antidiabetic drugs (OADs)
Length of follow up (if applicable)	

**Outcome measures/
Effect size**
	Type 1 DM:-
	
	a. HbA1c
	• **ILis (or ILisMix) versus HI (or HIMix)**
	
	  (All, 8,435 patients):-
	  Weighted mean difference (WMD) and 95% confidence interval (CI) = -0.09% (-0.16 to -0.01%) I²=41.9%
	
	    - Adult patients (7,102)
	    [WMD (95% CI)= -0.10% (-0.18 to -0.02%)] I²=40.6%
	
	    - Paediatric patients (1,333)
	    [WMD (95% CI)= -0.01% (-0.26 to 0.24%)] I²=53.0%
	
	• **IAsp (or IAspMix) versus HI (or HIMix)**
	
	  All, 2,948 patients:-
	  [WMD (95% CI)= -0.14 %(-0.22 to -0.07%)] I²=0.0%
	
	b. Blood Glucose
	
	  Eight-point blood glucose profiles
	  ILis or IAsp resulted in lower blood glucose profiles after meals (post-breakfast, post-lunch and post-dinner) compared with HI. Blood glucose levels before meals were higher with insulin analogues in some trials.
	
	• **Pre-prandial and postprandial blood glucose**
	
	  Ilis (or ILisMix) versus HI (or HIMix)
	  Fasting (233 patients):-
	  [WMD (95% CI)= -0.74 (-1.62 to 0.13)] I²=0.0%
	
	  Pre-prandial (2,014 patients):-
	  [WMD (95% CI)= 0.27 (-0.10 to 0.65)] I²=27.5%
	
	  1-hour postprandial (2,074 patients):-
	  [WMD (95% CI)= -1.06 (-1.60 to -0.52)] I²=0.0%
	
	  2-hour postprandial (2,210 patients):-
	  [WMD (95% CI)= -1.25 (-1.70 to -0.79)] I²=40.8%
	
	c. Mortality
	
	• 5 RCTs provided mortality data, 28 did not and 16 mentioned there were no deaths. None of the deaths were treatment related.
	
	d. Quality of life (QOL)
	
	ILis versus HI (16 trials)
	• Overall, type 1 patients prefer ILis compared to HI because of its convenience.
	• In terms of well being, there was limited evidence showing that ILis is better than HI.
	
	Type 2 DM:-
	a. HbA1c
	
	• **ILis (or ILisMix) versus HI (or HIXMix)**
	  All, 10 trials, 2,844 patients:-
	  [WMD (95% CI)= -0.11% (-0.22 to 0.00%)] I²=0.0%
	
	  IAsp versus HI (all, 6 trials, 750 patients):-
	  [WMD (95% CI)= -0.09% (-0.23 to 0.05%)] I²=0.0%
	
	  IGlu versus HI (all, 2 trials, 1,768 patients):-
	  [WMD (95% CI)= -0.03% (-0.18 to 0.11%)] I²=65.5%
	
	b. Blood Glucose
	
	• **Eight-point blood glucose profiles**
	  Limited and inconclusive evidence for blood glucose profiles in patients treated with IAsp versus HI or ILis versus HI.
	
	• **Pre-prandial and postprandial blood glucose**
	  Patients with type 2 diabetes treated with ILis or IAsp had a better control of postprandial blood glucose levels compared with HI or OADs.
	
	  No conclusive evidence was obtained for fasting and pre-prandial blood glucose levels.

Outcome measures/ Effect size (Con't)	**c. Mortality** • 5 RCTs provided mortality data, 27 did not and 7 mentioned there were no deaths. No consistency in reporting mortality data in the results. **d. Quality of life (QoL)** **ILis versus HI (2 trials)** • Did not show any differences in terms of treatment satisfaction or patients well being. **Gestational DM:-** **a. HbA1c:-** • (2 RCT reports, 91 patients) HbA1c level was higher with ILis: [WMD (95% CI)= 0.06% (-0.11 to 0.23%)] **b. Blood Glucose** • Pre-prandial and postprandial blood glucose (ILis versus HI, 2 trials):- No differences for pre-prandial blood glucose levels Significantly lower one-hour postprandial blood glucose levels of patients treated with ILis. **Authors conclusion:** In type 1 DM, treatment with ILis or IAsp significantly reduced HbA1c levels, compared to HI. For type 2 DM, treatment with short-acting insulin analogues did not demonstrate differences in HbA1c levels, compared with HI. Uncertainty remains regarding the use of short-acting insulin analogues in gestational DM patients and pregnant women with diabetes.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, RR, 95% CI 7.CI is not wide INAHTA checklist for HTA report

Evidence Table	: **Effectiveness**
Question	: **Is insulin analogues effective for treatment of diabetes mellitus compared to conventional human insulin?**

Bibliographic citation	2. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennet H. Efficacy and safety of insulin analogues for the management of diabetes mellitus; a meta-analysis. CMAJ.2009;180(4):285-297
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to compare the outcome of insulin analogues with conventional insulins in the treatment of type1, type 2 and gestational diabetes. Two earlier systematic reviews of the efficacy and safety of rapid-and long-acting insulin analogues (Barnajee *et al.* and Tran *et al.*, CADTH, 2007) were updated. Original search strategy used for the health technology assessments were updated to include studies published up to April 2007. Electronic searches of the MEDLINE (1966 to April 2007), MEDLINE In-Process and Other Non-Indexed Citations, MEDLINE Daily Update, EMBASE (1980 to April 2007), BIOSIS Previews (1989 to April 2007) and the Cochrane Library (Issue 3, 2007).Limited the search to randomised controlled trials. Grey literature was also searched. Studies selected based on inclusion criteria. Two reviewers independently assessed the methodological quality of the included studies of rapid -acting insulin analogues and another two reviewers assessed the included studies of long-acting analogues using Jadad scale. Each of the reviewers independently extracted data from the articles included in the analysis using a predesigned form. Data extraction at the study level was repeated for studies contained in the two original health technology assessments. Data were combined using random- effects model. An $I^2 \geq 50\%$ represent moderate heterogeneity and $I^2 \geq 75\%$ represent high level of heterogeneity.
LE	I
Number of patients & Patient characteristics	Rapid-acting insulin analogues:- • Selected 5 trials (total =68 RCTs for meta-analysis) Long-acting insulin analogues:- • Selected 20 and one trial was identified by stakeholders (total=49 RCTs for meta-analysis). • Most of the trials included were multinational and sponsored by industry. • Trial duration ranged from 4 weeks to 30 months. • Number of patients in each study ranged from 7 to 1,008. • Of the 48 crossover studies, most lacked or did not mention a washout period. • All studies were of open-label design. • Most trials was rated as poor (Jaded score 2 or 3) • No major differences across trials in terms of patients characteristics (e.g. sex, degree of obesity, and severity or duration of diabetes).
Intervention	Rapid-acting or Long-acting insulin analogues
Comparison	Conventional human insulin (HI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM:-**
	
	a. HbA1c (adult)
	(rapid-acting insulin analogues)
	• **Insulin lispro versus regular human insulin (22 trials, 6,021 patients):-**
	  [WMD (95% CI)= -0.09% (-0.16 to -0.02%)] I^2=0.0%
	
	• **Insulin aspart versus regular human insulin (7 trials, 3,035 patients):-**
	  [WMD (95% CI)= -0.13% (-0.20 to - 0.07%)] I^2=0.0%
	
	(long-acting insulin analogues)
	• **Insulin glargine versus NPH insulin (11 trials, 2,728 patients):-**
	  [WMD (95% CI)= -0.11% (-0.21 to -0.02%)] I^2=38.8%
	
	• **Insulin detemir versus NPH insulin (7 trials, 2,558 patients):-**
	  [WMD (95% CI)= -0.06% (-0.13 to 0.02%)] I^2=0.0%
	
	• **Insulin detemir + insulin aspart versus NPH + regular human insulin (1 trial, 595 patients):-**
	  [WMD (95% CI)= -0.23% (-0.37 to -0.09%)] I^2=NA

Outcome measures/ Effect size (Con't)	**b. HbA1c (children and adolescents)**
	
	(rapid-acting insulin analogues)
	
	• **Insulin lispro versus regular human insulin (children, 4 trials, 286 patients):-**
	  [WMD (95% CI)= 0.14% (-0.18 to 0.46%)] I^2=35.3%
	
	• **Insulin lispro versus regular human insulin (multiple daily injections only, adolescents, 1 trial, 926 patients):-**
	  [WMD (95% CI)= -0.01% (-0.21 to 0.19%)] I^2=NA
	
	(long-acting insulin analogues)
	
	• **Insulin glargine versus NPH insulin or insulin lente (children and adolescents, 4 trials, 680 patients):-**
	  [WMD (95% CI)= -0.25% (-0.55 to 0.05%)] I^2=61.8%
	
	• **Insulin glargine + insulin lispro versus NPH insulin + regular human insulin (adolescents,1 trial, 50 patients):-**
	  [WMD (95% CI)= -0.40% (-0.91 to 0.11%)] I^2=NA
	
	• **Insulin detemir versus NPH insulin (children and adolescents, 1 trial, 347 patients):-**
	  [WMD (95% CI)= 0.10% (-0.10 to 0.30%)] I^2=NA
	
	c. Quality of life (QoL)
	
	• No data on quality of life, patient satisfaction, diabetes-related complications or deaths were reported in any studies comparing insulin analogues with conventional insulin in children and adolescents.
	
	Type 2 DM
	
	HbA1c (adult)
	(rapid-acting insulin analogues)
	
	• **Insulin lispro versus regular human insulin (11 trials, 3,093 patients):-**
	  [WMD (95% CI)= -0.03% (-0.12 to 0.06%)] I^2=0.0%
	
	• **Insulin aspart versus regular human insulin (6 trials, 1,031 patients):-**
	  [WMD (95% CI)= -0.09% (-0.21 to 0.04%)] I^2=47.1%
	
	(long-acting insulin analogues)
	
	• **Insulin glargine versus NPH insulin (with oral antidiabetic therapy in both groups, 9 trials, 3,397 patients):-**
	  [WMD (95% CI)= -0.05% (-0.13 to 0.04%)] I^2=13.4%
	
	• **Insulin glargine versus NPH insulin (without oral antidiabetic therapy, 1 trial, 518 patients):-**
	  [WMD (95% CI)= 0.28% (0.07 to 0.49%)] I^2=NA
	
	• **Insulin detemir versus NPH insulin (with oral antidiabetic therapy in both groups, 3 trials, 1,159 patients):-**
	  [WMD (95% CI)= 0.13% (0.03 to 0.22%)] I^2=2.2%
	
	• **Insulin detemir versus NPH insulin (with insulin aspart before meals in both groups, 1 trial, 505 patients):-**
	  [WMD (95% CI)= 0.10% (-0.18 to 0.38%)] I^2=NA
	
	• **Insulin detemir + insulin aspart versus NPH + regular human insulin (1 trial, 394 patients):-**
	  [WMD (95% CI)= 0.06% (-0.31 to 0.19%)] I^2=NA
	
	Insufficient data available for comparisons between insulin analogues and conventional insulin in terms of diabetes-related complications or death.
	
	Pregnant women with diabetes:-
	a. Women with type 1 diabetes
	  HbA1c
	
	• **Insulin lispro versus regular human insulin:-**
	  [WMD (95% CI)= 0.20% (-1.03 to 1.43%)]
	
	b. Women with gestational diabetes
	  HbA1c
	
	• **Insulin lispro versus regular human insulin:-**
	  [WMD (95% CI)= 0.06% (-0.11 to 0.23%)]
	
	• Did not identify RCT of long-acting insulin analogues in pregnant women.
	
	Authors conclusion:
	Rapid- and long-acting insulin analogues offer little benefit relative to conventional insulin in terms of glycaemic control and reduced hypoglycaemia. Long-term, high quality studies are needed to determine whether insulin analogues reduce the risk of long-term complications of diabetes.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, 95% CI 7.CI is not wide

Evidence Table	**: Effectiveness**
Question	**: Is short-acting insulin analogues effective for treatment of diabetes mellitus compared to regular human insulin?**

Bibliographic citation	3. Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus (Review). Cochrane Database of systematic Reviews 2006, Issue 2. Edited (no change to conclusion), published in Issue 1, 2009.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to assess the effects of short acting insulin analogues versus regular human insulin. The Cochrane Library (issue 3, 2005), MEDLINE and EMBASE were searched. Additional searching by using cross-references from original articles, inquiries to pharmaceutical companies and contacted experts and approval agencies. Two reviewers independently selected trials for inclusion. Data from each included trial were extracted by two independent reviewers using data extraction form. The selection criteria include randomised controlled trials with an intervention duration of at least four weeks. Assessment for methodological quality was done using a modification of the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions and the criteria of Schulz and Jadad. Weighted mean differences (WMD) were calculated for the percentage of glycated haemoglobin and random effects model was used for the meta-analysis. Sensitivity analysis was performed.
LE	I

Number of patients & Patient characteristics	A total of 49 RCTs were included:-
	
	• Most of the studies were of poor methodological quality (88%), 12% were of higher quality
	• 17 of 42 included RCTs were of parallel design, the others had a crossover design.
	• 59% were multi-centres
	• Duration of intervention ranged from one to 12 months with mean follow-up of 3.6 months.
	• 8,274 participants took part in the 49 RCTs.
	  - 6,184 type 1 diabetic patients
	  - 2,028 type 2 diabetic patients
	  - 107 women with gestational diabetes

Intervention	Short-acting insulin analogues
Comparison	Regular human insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**a. HbA1c** **Type 1 DM:-** • **(Short acting insulin analogues versus regular human insulin, 22 studies):-** Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.10% (-0.16 to -0.05%)] I^2=47.0% **Subgroup analyses** • **Insulin Lispro versus regular human insulin, 15 studies)** [WMD (95% CI)= -0.11% (-0.18 to -0.04%)] I^2=49.0% • **Insulin Aspart versus regular human insulin, 6 studies)** [WMD (95% CI)= -0.11% (-0.19 to -0.03%)] I^2=20.0% **Types of intervention** • **(Continuous subcutaneous insulin injections (CSII)** [WMD (95% CI)= -0.20 %(-0.27 to -0.12%)] I^2=0.0% • **(Conventional intensified insulin therapy (IIT)** [WMD (95% CI)= -0.06% (-0.12 to 0.03%)] I^2=43.0%

Outcome measures/ Effect size (Con't)	**Duration of study**
	
	• (≤ 3 months)
	  [WMD (95% CI)= -0.07% (-0.16 to 0.02%)] I²=62.0%
	
	• (> 3 months)
	  [WMD (95% CI)= -0.12% (-0.17 to -0.07%)] I²=0.0%
	
	Type 2 DM:-
	
	• (Short acting insulin analogues versus regular human insulin, 5 studies):-
	  Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.03% (-0.11 to 0.04%)] I²=0.0%
	
	Children, adolescents, pregnant type 1 diabetic patients, patients with gestational diabetes
	
	• Prepubertal and adolescents with type 1 diabetes mellitus – no significant reduction in HbA1c
	
	• In pregnant women with type 1 diabetes – similar reduction in HbA1c
	
	• In gestational diabetes-no significant difference
	
	b. Quality of life (QoL)
	
	12 publications
	
	- 7 studies used the Diabetes Treatment Satisfaction Questionnaire, DTSQ
	
	- Of these, three studies found no significant difference between treatment arms while four observed improvement in the analogue arm
	
	Authors conclusion:
	
	Our analysis suggests sonly minor benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long term efficacy and safety data are available we suggest a cautious response to the vigorous promotion of insulin analogues.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, 95% CI 7. CI is not wide

Evidence Table	: **Effectiveness**
Question	: **Is short-acting insulin analogues (insulin lispro) effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	4. Brunetti P, Muggeo M, Cattin L, Arcangeli A, Pozzilli P, Provenzano V, Francesconi A, Calatola P, Santeusanio F. Incidence of severe nocturnal hypoglycaemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. Nutrition, Metabolism & Cardiovascular Diseases. 2010;20:519-526
Study Type / Methods	Randomised controlled trial (RCT) in Italy The objective of this study was to further investigate the pairing of insulin glargine with either RHI or lispro in Type 1 diabetes mellitus (DM) National, multicentre, randomised, parallel-group, open label, non-inferiority, Phase III trial. The study duration was 28 weeks including a 2-week running period, 8-week qualification phase, 16-week treatment phase and 2-week follow-up. Patients from hospitals or diabetes clinics were recruited through the referral of diabetologists who manage patients with type 1 DM in Italy. At the end of the qualification phase, patients were randomised (V4) in accordance with the randomisation sequence. The randomisation sequence was generated by the study biometrician and the investigators were not blinded to the randomisation list. Patients continued to receive insulin glargine at dinner time and were randomised to either regular human insulin (RHI) or lispro at each meal time.
LE	II-I

Number of patients & Patient characteristics	A total of 395 adults with type 1 diabetes mellitus were included:-
	
	   - 202 treated with glargine and RHI
	
	   - 193 treated with glargine and insulin lispro
	
	Baseline characteristics were similar between two groups:-
	• Insulin galrgine and RHI group [Mean± SD)]:-
	   - Age = 35.2 ± 10.5
	   - Diabetes duration (years) = 13.0 ± 8.8
	   - HbA1c (%) = 7.39 % ± 0.88
	   - FPG (mmol/L) = 10.4 ± 3.1
	   - 57.9% male, 42.1% female
	• Insulin galrgine and RHI group [Mean± SD)]:-
	   - Age = 35.3 ± 9.9
	   - Diabetes duration (years) = 13.0 ± 8.8
	   - HbA1c (%) = 7.39 % ± 0.97
	   - FPG (mmol/L) = 10.1 ± 2.8
	   - 64.8% male, 35.2% female

Intervention	Insulin glargine plus lispro
Comparison	Insulin glargine plus RHI
Length of follow up (if applicable)	28 weeks

Outcome measures/ Effect size	Overall, a total of 373 patients [192 (95.0%) in the RHI group and 181 (93.7%) in the lispro group] completed the study:-
	
	- Consent withdrawal was the main reason for early study discontinuation
	
	a. Glycaemic control at the end of the study
	
	• HbA1c (Mean ± SD):-
	
	  - RHI group (7.10 % ± 0.83%)
	
	  - Insulin lispro group (6.95 % ± 0.78%)
	
	  - No significant difference was observed between treatments (P > 0.05)
	
	• Fasting Plasma Glucose (Mean ± SD):-
	
	  - RHI group (164.6 mg/dL ± 42.4 mg/dL)
	
	  - Insulin lispro group (169.2 mg/dL ± 41.8 mg/dL)
	
	b. Seven-point profiles and mean amplitude of glucose excursion
	
	- There was a trend of lower post-prandial blood glucose levels in lispro group compared with RHI group
	
	- RHI group have lower pre-prandial blood glucose levels compared with the lispro group with exception of breakfast blood glucose levels
	
	- Mean amplitude of glycaemic excursion (MAGE index) was comparable for both treatment groups; 147.3 ± 52.6 and 136.7 ± 48.3 mg/dL for the RHI and lispro group respectively (P=0.7637)
	
	c. QoL measurements using Well-being Enquiry for Diabetics (WED) questionnaire:-
	
	- Mean WED score=2.09 ± 0.50 and 2.09 ± 0.49 for the RHI and lispro group
	
	d. Body weight, haematology or blood chemistry:-
	
	- No significant changes were observed in either treatment groups at any point of time
	
	Authors conclusion:
	
	The results from this study suggest that insulin glargine in combination with short-acting analog or RHI was associated with similar and low rate of nocturnal hypoglycaemia and glycaemic control, owing to the peakless once-daily evening insulin glargine injection in both arms.

General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

Evidence Table : **Effectiveness**

Question : **Is short-acting insulin analogues (insulin aspart) effective for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	5. Rys P, Pankiewicz O, Lach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: A systematic review. Diabetes & Metabolism. 2011;37:190-200
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to compare outcomes of treatment with insulin aspart (IAsp) and regular human insulin (RHI), as well as biphasic insulin aspart (BIAsp) and and biphasic human insulin preparations (BHI) in type 1 and type 2 diabetes mellitus patients. The MEDLINE, EMBASE, CENTRAL, and Centre for Reviews and Dissemination was systematically searched. The final search was carried out in July 2009. References listed in the retrieved articles were also used. Two reviewers independently identified the relevant abstracts and selected studies according to the criteria and extracted the data for analysis. The selection criteria include randomised controlled trials with an intervention duration of at least four weeks. The quality of RCTs was also assessed, using the parameters proposed by Jadad *et al.* Dichotomous data were pooled using relative risk (RR). Meta-analysis for continuous endpoints were expressed as weighted mean difference (WMD) or standardized mean difference (SMD). If, clinical trials were heterogenous ($P<0.01$), their results were pooled using a random-effects model.
LE	I
Number of patients & Patient characteristics	A total of 28 trials were included:- • 18 for type 1 DM • 11 for type 2 DM Type 1 DM:- • 14 involved adult patients • 4 included children and/or adolescents • 13 studies were RCTs with parallel design • 5 studies were RCTs with crossover design. • Only two studies were double blind • Allocation concealment was provided in three of the 18 studies • Mean HbA1c ranged from 6.9% to 9.6% Type 2 DM:- • 6 studies were RCTs with parallel design • 5 studies were RCTs with crossover design. • Only two studies were double blind • Allocation concealment was provided in one of the 11 studies • 11 trials included adult patients • Mean HbA1c ranged from 7.3% to 9.8% • Mean baseline BMI was between 28 kg/m^2 and 32 kg/m^2
Intervention	Insulin aspart (IAsp) or biphasic insulin aspart (BIAsp)
Comparison	Regular human insulin (RHI) or biphasic human insulin (BHI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM:-** **a. HbA1c** • **(13 studies):-** Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.11% (-0.16 to -0.06%)] I^2=17.5% **a. Post-breakfast glucose (5 studies, 2,820 patients)** • Weighted mean difference (WMD) and 95% confidence interval (CI) = [-1.43 mmol/L (-1.75 to -1.11 mmol/L)] I^2=NA **b. Post- lunch glucose (5 studies, 2,712 patients)** • Weighted mean difference (WMD) and 95% confidence interval (CI) = [-1.11 mmol/L (-1.61 to -0.61 mmol/L)] I^2=NA **c. Post-dinner glucose (6 studies, 3,138 patients)** • Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.97 mmol/L (-1.25 to -0.69 mmol/L)] I^2=NA **d. Fasting glucose (5 studies, 2,138 patients)** • Weighted mean difference (WMD) and 95% confidence interval (CI) = [0.15 mmol/L (-0.55 to 0.86 mmol/L)] I^2=NA **e. Treatment satisfaction** The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used to assess treatment satisfaction in three studies, but the part on treatment flexibility was assessed in only two of them. • **Total DTSQ:-** Standardized mean difference (SMD) and 95% confidence interval (CI) = [0.30 (0.20 to 0.40)] • **DTSQ treatment flexibility:-** Standardized mean difference (SMD) and 95% confidence interval (CI) = [0.31 (0.15 to 0.47)] **f. Quality of life (QOL)= 2 studies:-** • Using Diabetes-Specific-Quality of Life Scale (DSQOLS) concerning dietary restrictions, one study reported significant improvement in QOL in 23% of IAs group and 14% of the RHI group • The other study reported no significant difference in QOL based on Diabetes Health Profile (DHP) questionnaire **Type 2 DM:-** **a. HbA1c** • **(9 studies):-** Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.04% (-0.10 to 0.03%)] Cochran Q=13.14, p=0.107 **b. Post-prandial glucose (3 studies, 134 patients, daily mean PPG):-** • Weighted mean difference (WMD) and 95% confidence interval (CI)= [-1.18 mmol/L (-1.88 to -0.47 mmol/L)] I^2=NA **c. Post-breakfast glucose (3 studies, 512 patients):-** • Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.83 mmol/L (-1.45 to -0.21 mmol/l)] I^2=NA **d. Post-lunch glucose (2 studies, 225 patients):-** • Weighted mean difference (WMD) and 95% confidence interval (CI)= [-1.32 mmol/L (-2.16 to -0.49 mmol/L)] I^2=NA **e.Treatment satisfaction and quality of life:-** • No studies retrieved. **Authors conclusion:** Analysis based on a systematic review showed that treatment with IAsp in type 1 DM patients resulted in moderately better metabolic control and treatment satisfaction than RHI. In type 2 DM patients, meta-analysis showed improvement in post prandial glucose, but not in other outcomes.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6.WMD, SMD, 95% CI 7.CI is not wide

Evidence Table	**: Effectiveness**
Question	**: Is short-acting insulin analogues (insulin aspart) effective for treatment of diabetes mellitus in pregnant women compared to regular human insulin?**

Bibliographic citation	6. Mathiesen ER, Kinsley B, Amiel B, Ameil SA, Heller S, McCancre D, Duran S, Bellaire S, Raben A. Maternal glycemic control and hypoglycaemia in type 1 diabetic pregnancy. A randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care.2007;30 (4):771-776
Study Type / Methods	Randomised controlled trial (RCT) The objective of this study was to assess the safety and efficacy of insulin aspart (IAsp) versus regular human insulin (HI) in basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes. Subjects who were either pregnant with singleton pregnancy (gestational age $\leq$ 10 weeks) or planning to become pregnant were randomised (1:1) to IAsp or HI in combination with NPH insulin one to four times per day in an open-label, parallel-group study conducted at 63 sites in 18 countries, mainly within Europe. Subjects were allocated to the lowest available treatment number at each centre. Because study insulin injection timing varied, an open-label approach was used. Subjects had AIC $\leq$8% at confirmation of pregnancy. Subjects not pregnant at screening were withdrawn if not pregnant $\leq$12 months after randomisation. Insulin doses were titrated toward predefined glucose targets and AIC <6.5%. Subjects were recruited between September 2002 and August 2004; the last follow-up visit was in April 2005. In total, 412 subjects were randomised and treated. Of these 322 (IAsp, 157; HI, 165) were pregnant during the study. Outcome assessed included risk of major maternal hypoglycaemia, AIC, plasma glucose profiles , and maternal safety outcomes. Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire at randomisation and at follow-up visits. Subjects ranked 8 items on a 7-point Likert scale to measure overall treatment satisfaction (satisfaction with treatment, flexibility, diabetes understanding, convenience, and willingness to continue treatment and recommend treatment). Higher scale = greater treatment satisfaction.
LE	II-I

Number of patients & Patient characteristics	A total of 322 were included:-
	- 157 treated with insulin aspart
	- 165 treated with HI
	
	Baseline characteristics
	• IAsp group (Mean ± SD) or n (%):-
	  - Age = 29.0 ± 4.7
	  - Body mass index; 24.9 ± 4.0 kg/m^2
	  - Duration of diabetes (years) = 12.2 ± 7.1
	  - AIC (%) = 7.0 ± 0.8
	  - Retinopathy = 43 (27.4%)
	  - Neuropathy = 7 (4.5%)
	
	• HI group (Mean ± SD) :-
	  - Age = 29.0 ± 4.5
	  - Body mass index; 24.6 ± 3.7 kg/m^2
	  - Duration of diabetes (years) = 11.8 ± 7.4
	  - AIC (%) = 6.9 ± 1.0
	  - Retinopathy = 45 (27.3%)
	  - Neuropathy = 4 (2.4%)

Intervention	Short-acting insulin analogues (insulin aspart)
Comparison	Regular human insulin
Length of follow up (if applicable)	Maximum duration of participation was 22 months

Outcome measures/ Effect size	264 (81.98%) completed pregnancy and the trial intervention:- - Of the 58 non completers (IAsp, 24; HI, 34) 31 were withdrawn due to adverse events (IAsp, 14; HI, 17) - 27 for other reasons (IAsp, 10; HI, 17) **a. Glycaemic control** **AIC (HbA1c):-** • **At the end of second trimester (IAsp minus HI):-** Mean difference (MD) and 95% confidence interval (CI) = [-0.04% (-0.18 to 0.11%)] P= not significant (NS) • **At the end of third trimester (IAsp minus HI):-** Mean difference (MD) and 95% confidence interval (CI) = [-0.08% (-0.23 to 0.06%)] P= not significant (NS) • A total of 80% of subjects achieved an AIC ≤6.5%. **Average postprandial plasma glucose increments:-** • At the end of first and third trimesters, average postprandial plasma glucose increments were lower with IAsp than HI (P=0.003 and P=0.044) **Mean plasma glucose levels 90 min after breakfast:-** • At the end of first and third trimesters, average postprandial plasma glucose increments were lower with IAsp than HI (P=0.044 and P=0.001) **b. Quality of life (QoL) assessments** • **At follow-up, overall treatment satisfaction (IAsp versus HI):-** = (87.6 ± 12.0) versus (83.4 ± 15.3), P= 0.031. • **At follow-up, satisfaction with flexible treatment (IAsp versus HI):-** = (85.9 ± 15.0) versus (75.8 ± 23.8) • **At follow-up, willingness to continue on present treatment (IAsp versus HI):-** = (90.1 ± 16.2) versus (81.9 ± 25.2) **Authors conclusion:** IAsp is at least as safe and effective as HI when used in basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes and may potentially offer some benefits in terms of postprandial glucose control and preventing severe hypoglycaemia.
General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

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Evidence Table : **Effectiveness**

Question : **Is short-acting insulin analogues (insulin aspart) effective for treatment of diabetes mellitus in pregnant women compared to regular human insulin?**

Bibliographic citation	7. Pettitt DJ, Ospina P, Howard C, Zisser H, Jovanoic L. Efficacy, safety and lack of immunogenecity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. Diabet. Med. 2007; 24: 1129-1135
Study Type / Methods	Randomised controlled trial (RCT) in the United States of America The objective of this study was to assess the efficacy and safety of insulin aspart (IAsp) compared with regular human insulin (HI) as a bolus component of basal-bolus therapy for subjects with gestational diabetes mellitus (GDM). In this single-centre, randomised, parallel group, open-label trial, 27 women with GDM were randomised to receive either IAsp, 5 minutes before meal or regular human insulin. The trial period extended from diagnosis of insulin requiring GDM (18 to 28th week of pregnancy) to 6 weeks postpartum.
LE	II-I

Number of patients & Patient characteristics	A total of 27 women were included:-
	- 14 treated with insulin aspart
	- 13 treated with HI
	
	Baseline characteristics
	• IAsp group (Mean ± SD):-
	  - Age = 31.6 ± 5.9
	  - Body mass index; 24.3 ± 4.7 kg/m^2
	  - HbA1c (%) =5.1 ± 0.4
	
	• HI group (Mean ± SD) :-
	  - Age = 29.7 ± 6.9
	  - Body mass index; 33.2 ± 5.7 kg/m^2
	  - HbA1c (%) =5.3 ± 0.3

Intervention	Short-acting insulin analogues (insulin aspart)
Comparison	Regular human insulin
Length of follow up (if applicable)	From 18 to 28th week of pregnancy to 6 weeks postpartum.

Outcome measures/ Effect size	13 (93%) subjects in the IAsp and 9 (69%) in the HI group completed the study:-
	- Four subjects discontinued the study since they delivered early and one subject discontinued the study due to the inability during the meal test to provide adequate blood samples because of excessive clotting.
	
	a. Glycaemic control
	• Both treatment groups maintained good overall glycaemic control during the study (beginning and end of study HbA1c ≤ 6%).
	
	• Mean ± SD glucose at week 6:-
	  - IAsp (4.2 ± 0.57 mmol/L)
	  - HI (4.8 ± 0.86 mmol/L)
	
	• Change from baseline values (Mean ± SD) for glucose at week 6:-
	  - IAsp (-1.09 ± 0.54 mmol/L)
	  - HI (-0.54 ± 0.74 mmol
	
	Authors conclusion:
	IAsp was more effective than HI in decreasing postprandial glucose concentrations. Overall safety and effectiveness of IAsp were comparable to HI in pregnant women with GDM.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Effectiveness**

Question : **Is short-acting insulin analogues effective for treatment of diabetes mellitus compared to regular human insulin?**

Bibliographic citation	8. Plank J, Siebenhofer A, Berghold A, Jeitler K, Horvath K, Mrak P, Pieber TR. Systematic Review and Meta-analysis of Short-acting Insulin Analogues in patients with Diabetes Mellitus. Arch Intern Med. 2005;165:1337-1344
Study Type / Methods	Systematic Review and meta-analysis

The objective of this review was to provide information on glucose control, hypoglycaemia, quality of life, and diabetes-specific complications of short acting insulin analogues compared with regular insulin.

The Cochrane Library (issue 4, 2003), MEDLINE (January 1966 to December 2003), and EMBASE (January 1974 to December 2003) were searched. Additional searching by using reference lists and abstracts books from major diabetology meetings from 1992 to 2003, contacted three main insulin producing companies and checked bibliographies of textbooks and relevant retrieved articles. Authors and experts were also contacted.

Two reviewers independently selected trials for inclusion. Data from each included trial were extracted by two independent reviewers using data extraction form. The selection criteria include randomised controlled trials with an intervention duration of at least four weeks.

Assessment for methodological quality was done using a modification of the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions and the criteria of Schulz *et al.* and Jadad *et al.*

Weighted mean differences (WMD) were calculated for the percentage of glycosylated haemoglobin and random effects model was used for the meta-analysis. Sensitivity analysis was performed. |
| **LE** | I |
| **Number of patients & Patient characteristics** | A total of 42 RCTs were included:-
- 7,933 participants took part in the 42 RCTs:-
   - 5,925 type 1 diabetes mellitus
   - 1,901 patients with the type 2 diabetes mellitus
   - 107 women with gestational diabetes

- Type 1 diabetes mellitus patients:-
   - Weighted mean age; 46 years
   - Diabetes duration;14 years
   - Body mass index; 24.4 kg/m^2

- Type 2 diabetes mellitus patients:-
   - Weighted mean age; 58 years
   - Diabetes duration;12 years
   - Body mass index; 28.2 kg/m^2

- Seven studies were of higher methodological qualities

RCTs included in Meta-analysis
- HbA1c:-
   - 20 trials with type 1 diabetic patients
   - 4 trials including type 2 diabetic patients

- Overall hypoglycaemia:-
   - 9 trials with type 1 diabetic patients
   - 5 trials including type 2 diabetic patients |

Intervention	Short-acting insulin analogues
Comparison	Regular human insulin
Length of follow up (if applicable)	

Outcome measures/ Effect size	**a. HbA1c**
	
	Type 1 DM:-
	
	• **(Short acting insulin analogues versus regular human insulin, 20 studies):-** Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.12% (-0.17 to -0.07%)]
	
	Type 2 DM:-
	
	• **(Short acting insulin analogues versus regular human insulin, 4 studies):-** Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.02% (-0.10 to 0.07%)]
	
	Children, adolescents, pregnant type 1 diabetic patients, patients with gestational diabetes
	
	• Prepubertal and adolescents with type 1 diabetes mellitus – no significant reduction in HbA1c
	
	• In pregnant women with type 1 diabetes mellitus, the reduction in HbA1c levels in the analogue and regular human insulin group was similar
	
	• In gestational diabetes-no significant difference
	
	b. Quality of life (QOL)
	
	• **11 trials reported data on quality of life:-**
	
	  - 7 studies used the Diabetes Treatment satisfaction Questionnaire (DTSQ), of these, three studies found no significant difference between treatment arms while four observed improvement in the analogue arm
	
	  - In 2 studies that assessed the quality of life in patients with type 2 diabetes mellitus, no difference was observed between treatments.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, 95% CI 7. CI is not wide

Evidence Table	**: Effectiveness**
Question	**: Is long-acting insulin analogues effective for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	9. Tran K, Barnajee S, Li H, Cimon K, Daneman D, Simpson SH, Campbell K. Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness. Technology report No 92. Ottawa: Canadian Agency for drugs and Technologies in Health, 2007.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to evaluate the clinical efficacy and economic implications of long-acting insulin analogues, specifically insulin glargine (IGlar) and insulin determir (IDet), for the treatment of diabetes mellitus (DM). Electronic searches of the MEDLINE, BIOSIS Previews, PASCAL, EMBASE and the Cochrane Database of Systematic Reviews from 1990 until February 2006. Grey literature was also searched. Two of the three reviewers independently selected trials for inclusion. Data from each included trial were extracted by one reviewer using a structured form. Another reviewer checked the data independently. The quality of the included RCTs was evaluated using the Jadad five-point scale. Cochrane software Review Manager 4.2.3 was used to analyse data and generate forest plots. If I^2 >75% the studies were not pooled. A review of economic studies and budget impact analysis were performed
LE	I
Number of patients & Patient characteristics	A total of 34 RCTs were included:- • 23 on type 1 DM • 11 on type 2 DM • No RCTS on gestational DM Mean Jadad score with standard deviation (SD) for RCTs reports on type 1 DM was 2.3±0.7 and on type 2 DM was 2.4±0.7. RCTs on type 1 DM:- • Number of patients in the trials varied between 14 and 749 • 1 involved paediatric and young adults (ages from 8 to 21 years) • 2 involved only paediatric (mean age 12 years) • 20 involved adults (mean age between 24 to 43 years) • Mean duration of diabetes ranged between 4.8 and 5.0 years RCTs on type 2 DM:- • Mean age (between 53 and 61 years) • Mean duration of diabetes ranged between 8.5 and 13.8 years
Intervention	Long-acting insulin analogues (IGar or IDet)
Comparison	Conventional human insulin (HI) or oral antidiabetic drugs (OADs)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM:-**
	
	a. HbA1c
	
	• **IGlar versus Neutral Protamine Hagedorn (NPH), (bolus all, 11 trials, 3,279 patients):-**
	  - WMD not pooled, I^2=78.5%
	  HbA1c levels were lowered to a greater degree in IGlar group compared to NPH group in some trials but not in others.
	  - Difference not clinically important, because a difference in HbA1c of 1.0% is considered to be a minimal clinical change.
	
	• **IDet versus NPH (bolus all, 8 trials, 2,937 patients):-** [WMD (95% CI)= -0.05% (-0.12 to 0.03%)] I^2=0.0%
	
	b. Blood Glucose
	
	• **Eight-point blood glucose profiles**
	  Remains uncertain whether the effect of long-acting insulin analogues on eight-point glucose profiles is robust, compared with NPH.

<table>
<tr>
<td rowspan="1">Outcome measures/
Effect size (Con't)</td>
<td>

- Fasting plasma glucose
  IGlar versus NPH (bolus all, 6 trials, 1,682 patients)
  WMD (95% CI)= -0.92 (-1.21 to -0.63)] I²=18.9%

- **IDet versus NPH (bolus all, 6 trials, 2,362 patients)**
  [WMD (95% CI)= -0.87 (-1.27 to -0.46)] I²=49.1%

c. Mortality

- 3 RCTs reported on mortality data
  - 1 RCT- reported 1 death in the NPH arm (cause unrelated to the study medication)
  - 1 RCT- reported 1 death in the IDet arm (cause unknown)
  - 1 RCT- reported no deaths in IGlar or NPH arm

d. Quality of life (QoL)

- **IGlar versus NPH or ultra lente (2 RCTs)**
  - I RCT reported patients being treated with IGlar showed no statistically significant difference in fear of hypoglycaemia compared with NPH patients (mean ± SD: 1.8±0.13 versus 1.7±0.13, p=0.44).
  - 1 RCT reported that the scores on all items (satisfaction, convenience, flexibility, and willingness to continue) in the Diabetes Treatment Satisfaction Questionnaire (DTSQ) were statistically significantly better with IGlar than with NPH. In the Well-Being Questionnaire (WBQ), there was no statistically significant difference.

Type 2 DM:-

a. HbA1c

- **IGlar versus NPH (all, 7 trials, 2,967 patients):-**
  [WMD (95% CI)= 0.05% (-0.07 to 0.16%)] I²=45.9%

- **IDet versus NPH (all, 8 trials, 2,937 patients):-**
  [WMD (95% CI)= 0.11% (-0.03 to 0.26%)] I²=0.0%

b. Blood Glucose

- **Eight-point blood glucose profiles**

  IGlar versus NPH:-
  No statistically significant difference between treatments.

  IGlar versus NPH:-
  Similar in both treatments when IAsp was used as the bolus or treatment was supplemented with OAD.

- **Fasting plasma glucose**
  No significant difference between IGlar and NPH treatments or between IDet and NPH treatments.

c. Mortality

- 5 RCTs reported mortality data.
  5 deaths in the IGlar arm and 7 deaths in the NPH arm. None of the deaths were related to the study medication.

d. Quality of life (QoL)

- None of the RCTs on type 2 DM reported on QoL data.

Authors conclusion:

Long-acting insulin analogues have not demonstrated clinically important differences in glycated haemoglobin, a widely used marker of blood sugar control in types 1 and 2 DM. Significant reduction in fasting plasma glucose in type 1 DM in IGlar group and the IDet group compared with NPH group.

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<td>General comments</td>
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Quality assessment (CASP)

1. Yes
2. Yes
3. Yes
4. Yes
5. Yes
6. WMD, RR, 95% CI
7. CI is not wide

INAHTA checklist for HTA report

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Evidence Table : **Effectiveness**

Question : **Is long-acting insulin analogue (insulin glargine) effective for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	10. Warren W, Weatherly-Jones E, Chilcott J, Beverly C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technology Assessment 2004;8(45). Health Technology Assessment NHS R&D HTA programme.
Study Type / Methods	Systematic Review The objective of this review was to evaluate the use of insulin glargine in its licensed basal-bolus indication in terms of both clinical and cost-effectiveness. Fourteen electronic bibliographic databases were searched; biological abstracts, CINAHL, Cochrane database, EMBASE, HTA database, MEDLINE, NHS Economic Evaluations Database (NHS EED), OHE Health Economic Evaluation Database, PreMedline, Science Citation Index and Social Sciences Citation Index. No restrictions were applied. Search undertaken until 2002. Data extraction was done by one reviewer. Quality scores for each of the included RCTs were assigned according to the Jadad scale. Length of study was at least 4 weeks. Economic review is based solely on review of economic model provided in the Aventis submission.
LE	I

Number of patients & Patient characteristics	13 studies met the inclusion criteria:-
	• 8 studies for type 1 DM
	  - 4 full texts
	  - 4 abstracts
	• 5 studies for type 2 DM
	  - 2 full texts
	  - 3 abstracts
	• All were prospective studies, nine were described as RCTs.
	• None of the trials were double blinded, but two compared two formulations of insulin glargine with NPH using partially blinded designs.

Intervention	Long-acting insulin analogues (Insulin Glargine)
Comparison	Other long acting basal insulin [Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	
Outcome measures/ Effect size	Formal meta-analyses of results of studies was not possible as insufficient raw data were available and studies described were of different durations and therefore not directly comparable in terms of their effects on the indices of glycaemic control. **Type 1 DM:-** **Summary of evidence** • Insulin glargine appears to be more effective than NPH in reducing fasting blood glucose (FBG) but not in reducing HbA1c and there was some evidence that both insulins are as effective as each other in both FBG and HbA1c control. **Type 2 DM:-** **Summary of evidence** • There was no evidence that insulin glargine was more effective than NPH in reducing either FBG or HbA1c and some evidence that both insulins were as effective as each other in both FBG and HbA1c control.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Mean and P value 7. CI not mentioned INAHTA checklist for HTA report

Evidence Table : **Effectiveness**

Question : **Is long-acting insulin analogues (insulin glargine) effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	11. Bolli BG, Songini M, Trovati M, Prato SD, Ghirlanda G, Cordera R, Trevisan R, G Riccardi, Noacco C. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes. Nutrition, Metabolism & Cardiovascular Diseases.2009;19:571-579
Study Type / Methods	Randomised controlled trial (RCT) in Italy The aim of this study was to establish glycaemic control in subjects with type 1 DM treated with basal insulin glargine as compared to NPH. Randomised, parallel group, open-label, multicentre (21 centres), single country study with a 30-week duration (4 week run in phase, 24-week treatment period and 2-week safety assessment). Subjects were randomised during screening to receive either glargine once daily at dinner time or NPH twice (or more) daily (bedtime and lunch) as basal insulin in basal-bolus intensive treatment for type 1 DM patients with insulin lispro as bolus insulin. During the last 2 weeks before the scheduled visit s patients measured BG 2 hour after meals and at 3 a.m., in addition to FBG and pre-prandial BG, to provide 7-point BG profiles to calculate mean daily blood glucose (MDBG) and mean amplitude glucose excursion (MAGE). Participants were to complete the well-being Enquiry for Diabetics (WED) questionnaire at the randomisation visit (week 0) at 12 and at 24 weeks of treatment phase. Episodes of hypoglycaemia and adverse events (AEs) were recorded by the participants in diaries and reported to the investigator at each visit.
LE	II-I
Number of patients & Patient characteristics	A total of 175 adults with type 1 diabetes mellitus were included:- - 85 treated with glargine plus insulin lipro - 90 treated with NPH insulin plus insulin lispro Baseline characteristics were similar between two groups:- • Insulin glargine group [Mean± SD)]:- - Age (years) = 35.5 ± 10.6 - 48 male, 37 female - Diabetes duration (years) = 12.9 ± 8.3 - HbA1c (%) = 7.8 % ± 0.7 - Weight (kg) = 67.5 ± 9.4 - Duration of intensive insulin therapy (years) = 8.3 ± 5.6 • NPH insulin group (Mean ± SD):- - Age (years)= 37.0 ± 9.4 - 49 male, 41 female - Diabetes duration (years) = 14.8 ± 9.6 - HbA1c (%) = 7.8 % ± 0.6 - Weight (kg) = 68.4 ± 10.4 - Duration of intensive insulin therapy (years) = 9.4 ± 6.5
Intervention	Insulin glargine plus insulin lispro
Comparison	NPH insulin plus insulin lispro
Length of follow up (if applicable)	30 weeks

Outcome measures/ Effect size	Overall, a total of 152 patients completed the study [78 (91.8%) in the insulin glargine group and 74 (82.2%) in the NPH insulin group] completed the study:-
	
	 - In the glargine group, 4 criteria violations, 2 protocol violations and I consent withdrawn were the reasons for discontinuations.
	
	 - In the NPH group, 3 criteria violations,3 consent withdrawn, 2 poor compliance, 2 lost to follow-up, 1 protocol violation and I other reason, were the reasons for discontinuations
	
	 At the end of the study:-
	
	 a. Glycaemic control (baseline to endpoint change)
	
	 • HbA1c (Mean ± 95% CI):-
	
	   - Insulin glargine group = [-0.56 % (-0.74 to -0.38%), P <0.0001
	
	   - Insulin NPH group = [-0.56 % (-0.75 to -0.37%), P <0.001
	
	 • Fasting Plasma Glucose (Mean ± 95% CI):-
	
	   - Insulin glargine group = [-28.0 mg/dL (-37.3 to -18.7 mg/dL, P< 0.001)
	
	   - Insulin NPH group = [-9.8 mg/dL(-19.1 to -0.5mg/dL P< 0.00374)
	
	   - Mean difference between the two treatment = [-18.2 mg/dL (-31.3 to -5.2 mg/dL), P <0.0064
	
	 • Mean daily blood glucose (MDBG), Mean ± 95% CI:-
	
	   - Insulin glargine group = [-10.1 mg/dL (-18.1 to -2.1 mg/dL, P< 0.0126)
	
	   - Insulin NPH group = no significant difference, P =0.1564
	
	 • Mean amplitude glucose excursion (MAGE), Mean ± 95% CI:-
	
	   - Insulin glargine group = [-20.0 mg/dL (-34.5 to - 5.9 mg/dL, P< 0.0056)
	
	   - Insulin NPH group = no significant difference, P = 0.6416
	
	 b. Insulin dose
	
	 • Total daily insulin injections (prandial plus basal insulin (mean ± SD):-
	
	   - Insulin glargine group, 4± 0.0
	
	   - NPH insulin group, 5.2± 0.5
	
	 c. Quality of life
	
	   - No statistically significant differences were observed from baseline in any of the domains in either group at 3 and 6 months.
	
	 Authors conclusion:
	
	 Switching from NPH to glargine is well tolerated and results into lower FBG, and lower glucose variability while reducing hypoglycaemia.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Effectiveness**

Question : **Is long-acting insulin analogues (insulin glargine) effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	12. Chase HP, Arsalanian S, White NH, Tambolane WV. Insulin Glargine versus Intermediate acting insulin as the basal component of multiple daily injection regimes for adolescents with type 1 diabetes mellitus.J Paediatr. 2008;153:547-553
Study Type / Methods	Randomised controlled trial (RCT) in United States The objective of this study was to compare long-acting insulin glargine with intermediate-acting insulin NPH/Lente when used as the basal component of a multiple daily injection (MDM) regimen with prandial insulin lispro in adolescents with type 1 diabetes mellitus (DM) Active-controlled, randomised (1:1) open-label, sex-stratified, 2-arm, parallel-group study. After educational run-in period, patients were randomised to either stay on their existing basal insulin (NPH/Lente insulin twice daily) or to receive the once-daily morning glargine as basal therapy as part of multiple daily injection (MDI) regimen using insulin lispro as the prandial component in both treatment groups. Everyday throughout the treatment period, each patient recorded his or her fasting, preprandial, and bedtime self-monitored blood glucose (SMBG) Study outcome were documented during clinic visit.
LE	II-I

Number of patients & Patient characteristics	A total of 175 adolescents with type 1 diabetes mellitus were included:-
	- 85 treated with glargine plus insulin lipro
	- 90 treated with NPH insulin plus insulin lispro
	Baseline characteristics were similar between two groups:-
	
	• Insulin glargine group [Mean (SD)]:-
	  - Age (years) = 13.1(2.4)
	  - 47.4% male, 53.6% female
	  - Diabetes duration (years) = 5.1 (3.4)
	  - HbA1c (%) = 7.8 % (0.8)
	  - Weight (kg) = 57.2 (14.8)
	
	• NPH insulin group [Mean (SD)]:-
	  - Age (years) = 13.4 (2.4)
	  - 47.6% male, 52.4% female
	  - Diabetes duration (years) = 5.4 (3.7)
	  - HbA1c (%) = 8.0 % (0.8)
	  - Weight (kg) = 59.1 (18.1)

Intervention	Insulin glargine plus insulin lispro
Comparison	NPH /Lente insulin plus insulin lispro
Length of follow up (if applicable)	24 weeks

Outcome measures/ Effect size	Overall, a total of 157 patients (89.7%) completed the study (per protocol population). [76 (89.4%) in the insulin glargine group and 81 (90.0%) in the NPH insulin group] completed the study:-
	
	 - In the glargine group, one had no baseline HbA1c, four treatment duration <148 days, four major protocol violations.
	
	 - In the NPH group, four no baseline HBA1c, two no post treatment HbA1c, one treatment duration < 148 days and two major protocol violations.
	
	 At the end of the study:-
	
	 a. Glycaemic control (baseline to endpoint change)
	
	 • HbA1c (Overall mean change ± SD):-
	
	   - Insulin glargine group = - 0.25 % ± 0.14%
	
	   - Insulin NPH group = - 0.05 % ± 0.13%
	
	   - Mean difference between IGlar and NPH/Lente, $p=0.1725$
	
	 However, an analysis of covariance, adjusting for baseline HbA1c, revealed a strong study arm effect on the slopes of the regression lines, indicating that the reduction in HbA1c was significantly greater with insulin glargine in those patients with higher baseline HbA1c values.
	
	 b. Insulin dose
	
	 • At study end points, daily insulin:-
	
	   - Insulin glargine group, received a total of 72.7 Units daily
	
	   - Insulin NPH group, received a total of 76.4 Units daily
	
	 Authors conclusion
	
	 Insulin glargine is well tolerated in MDI regimens for paediatric patients with type 1 DM and may be more efficacious than NPH/ Lente in those with elevated HbA1c

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Bibliographic citation	LEESII-Ion

Outcome measures/ Effect size	**ADDQoL** Present QoL score for the whole study sample at baseline was 1.3 ± 1.1 (Mean ± SD) reflecting good rather than very good or excellent. - Present QoL improved with glargine plus lispro but did not change with NPH plus human insulin [end point scores;1.6 ± 0.1 (mean ± SEM) versus1.3± 0.1, difference 0.3 (95% CI; 0.1 to 0.6, P=0.014) • The average weighted impact score (AWI) at baseline was −1.8 ± 1.2, (Mean ± SD) indicating an overall negative impact of diabetes on QoL - AWI score improved significantly with glargine plus lispro but changed little with NPH plus human insulin [-1.4 ± 0.1 (mean ± SEM) versus -1.7 ± 0.1, difference 0.3 (95% CI; 0.0 to 0.6, P=0.033 • Treatment satisfaction (DTSQ 36-0 scale score) at end point was markedly greater with glargine plus lispro compared with that of NPH plus human insulin (32.2 ± 3.4 versus 23.9 ± 7.2, mean difference 8.6 (95% CI; 6.5 to 10.6, P< 0.001). - Significant differences favouring glargine plus lispro were found for five of six items of the treatment satisfaction scale; current satisfaction with treatment (5.4 ± 0.2 versus 3.8 ± 0.2, P<0.001), convenience of treatment (5.3 ± 0.1 versus 4.1 ± 0.1, P<0.001), flexibility of treatment (5.2 ± 0.1 versus 3.9 ± 0.2, P<0.001), recommend to others and satisfaction to continue current treatment. **Authors conclusion** Insulin glargine plus insulin lispro improves treatment satisfaction, reduces the negative impact of diabetes QoL, and improves QoL in comparison with NPH insulin plus unmodified human insulin.
General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

Evidence Table	: Effectiveness
Question	: Is long-acting insulin analogues effective for treatment of type 2 diabetes mellitus compared to human insulin?

Bibliographic citation	14. Horvath K, Jeitler K, Berghold A, Horvath K, Ebrahim SH, Gratzer TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A. Lon-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes diabetes mellitus (Review). Cochrane Database of systematic Reviews 2007, Issue 2. Edited (no change to conclusion), published in Issue 4, 2009.
Study Type / Methods	Systematic Review and meta-analysis

The objective of this review was to assess the effects of long-term treatment with long-acting insulin analogues (insulin glargine and insulin detemir) compared with NPH insulin in patients with type 2 diabetes mellitus.

The Cochrane Library [including the Cochrane Controlled Trials Register (CENTRAL)], MEDLINE, EMBASE and CRD Databases (DARE, NHSEED, HTA) via Ovid Web Gateway were searched. Additional searching by using cross-references from original articles, inquiries to pharmaceutical companies and contacted experts and approval agencies.

Two authors independently selected trials for inclusion. Data from each included trial were extracted by two independent authors using data extraction form. The selection criteria include randomised controlled trials in adults with diabetes mellitus type 2 and had a trial duration of at least 24 weeks.

Assessment for methodological quality was done using a modification of the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions and the criteria of Schulz and Jadad.

Weighted mean differences (WMD) were calculated for the percentage of glycosylated haemoglobin and random effects model was used for the meta-analysis. Sensitivity analysis was performed. |
| **LE** | I |
| **Number of patients & Patient characteristics** | A total of 8 studies were included:-
- 6 studies investigated insulin glargine
- 2 studies investigated insulin determir
- 1,715 patients were randomised to insulin glargine
- 578 patients were randomised to insulin detemir
- Mean duration of diabetes ranged from 8 to 14 years
- Mean age ranging from 55 to 62 years
- Most patients were overweight, BMI ranging from 27 to 33 kg/m2
- Duration of included studies ranged from 24 to 52 weeks
- All include trials had a multi-centre design ranging from 7 to 111 centres. |
Intervention	Long-acting insulin analogues (insulin glargine or insulin detemir)
Comparison	NPH insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**a. HbA1c**

Weighted mean difference of change of HbA1c from baseline to study endpoint
- **(Glargine versus NPH, 4 studies 1,568 patients):-**
  Weighted mean difference (WMD) and 95% confidence interval (CI) = [0.05% (-0.08 to 0.17%)] I^2=0.0%
- **Insulin detemir versus NPH, 2 studies, 967 patients)**
  [WMD (95% CI)= 0.12% (0.01 to 0.23%)] I^2=0.0%, favouring NPH

b. Quality of life (QoL)
- No trial reported on quality of life
- Only one trial reported results on treatment satisfaction with Diabetes Treatment and satisfaction Questionnaire (DTSQc), more pronounced improvement of mean scores of treatment satisfaction was reported for treatment with insulin glargine versus NPH insulin |
| **General comments** | Quality assessment (CASP)
1. Yes
2. Yes
3. Yes
4. Yes
5. Yes
6. WMD, RR, 95% CI
7. CI is not wide |

Evidence Table	**: Effectiveness**
Question	**: Is long- acting insulin analogues effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	15. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment 2010; Vol. 14:No. 36. Health Technology Assessment NIHR HTA programme.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to review the newer agents available for blood glucose control in type 2 diabetes from four classes: the glucagon-like peptide (GLP-1) analogue exenatide; dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin and vildagliptin; the long- acting insulin analogues, glargine and determir; and to review concerns about the safety of thiazolidinediones. Databases searched: MEDLINE (1990-April 2008), EMBASE (1990-April 2008), the Cochrane Library (all sections) Issue 2, 2008, and the Science Citation Index and ISI Proceedings 2000-April 2008). Identify good quality systematic reviews and then looked for new trials published since the reviews. Combined the new trials with the relevant older ones in an updated meta-analyses. Data extraction was carried out by one person and checked by a second. Studies were assessed for quality using standard methods for reviews of trials.Meta-analyses were carried out using the Cochrane Review Manager (Revman) software.Modelling of cost-effectiveness of the various regimes used the United kingdom Prospective Diabetes Study (UKPDS) Outcomes Model.
LE	I
Number of patients & Patient characteristics	3 Good quality systematic reviews:- • Horvath *et al.* (Cochrane review, 2007) • Tran *et al.* (CADTH, 2007) • Warren *et al.* (UK HTA, 2004) The 3 systematic reviews included 14 RCTs of insulin Glargine and 2 RCTs of insulin Detemir. Three new RCTs identified:- • Montana (2007) • Philis-Tsimikas (2006) • Rosenstock (2008)
Intervention	Long-acting insulin analogues (IGar or IDet)
Comparison	Conventional human insulin (HI) or oral antidiabetic drugs (OADs)
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Type 2 DM:-** **a. HbA1c** • **IGlar versus NPH (10 trials, 3,915 patients):-** [WMD (95% CI)= 0.00% (-0.11 to 0.10%)] I^2=52.0% • **IDet versus NPH (4 trials, 1,584 patients):-** [WMD (95% CI)= 0.07% (-0.03 to 0.18%)] I2=0.0% **b. Weight change** • The glargine groups (8 studies) gained 0.23kg less weight than the NPH groups (range -1.10 to +0.23kg). Meta-analysis could not be performed, too many missing standard deviations). • The detemir groups (4 studies) gained 1.20kg less weight than the NPH groups (range -0.8 to -1.6kg). However, Meta-analysis could not be performed, too many missing standard deviations). **c. Health related quality of life** Not reported by any of the trials. **Authors conclusion** Glargine and detemir are equivalent to NPH in terms of glycaemic control as reflected in HbA1c level, but have modest advantages in terms of hypoglycaemia, especially nocturnal.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, 95% CI 7. CI is not wide INAHTA checklist for HTA report

Evidence Table : **Effectiveness**
Question : **Is long-acting insulin analogue (insulin glargine) effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	16. Bazzano LA, Lee LJ, Shi L, Reynolds K, Jackson JA, Fonseca V. Safety and efficacy of glargine compared with NPH insulin for treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetic Medicine.2008;25:924-932
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to systematically analyse evidence from RCTs examining the safety and efficacy of glargine and NPH insulin in adults with Type 2 diabetes. Electronic databases were searched; MEDLINE (1966 to March 2007), EMBASE (1974 to March 2007), and the Cochrane Central Register of Controlled Trials. Search was restricted to include only human studies. No language restriction. A manual search of references cited and contacted experts in the field. Contents of abstracts and full-text identified were reviewed independently by two investigators. Studies were eligible for inclusion if they met all the inclusion and exclusion criteria. The intervention duration was at least 4 weeks. Data abstraction was completed by two independent investigators. All analyses were conducted in STATA version 8.2. Meta-analysis was conducted according to the QUOROM guidelines for the conduct and reporting of meta-analysis of RCTs.
LE	I
Number of patients & Patient characteristics	12 trials were included:- • 4,385 participants • 54.1% were male • Mean age was 58.3 years • Mean BMI was 28.4 kg/m • Mean duration of diabetes was 10.5 years • The average length of studies was 27.8 weeks, with a range of 4 to 52 weeks • Average study size was 366 participants with a range of 24 to 756 participants
Intervention	Long-acting insulin analogue (Insulin glargine)
Comparison	[Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Type 2 DM (Insulin glargine versus NPH):-** **Mean net changes and 95%CI** (positive values favouring glargine and negative values favouring NPH) **a. HbA1c** • **(12 trials)** [Mean net change (95% CI)= 0.08% (-0.04 to 0.21%)] **b. Fasting plasma glucose (FPG)** • **(11 trials):-** [Mean net change (95% CI)= 0.21 mmol/L (-0.02 to 0.45 mmol/L)] **c. Body weight** • **(6 trials)** [Mean net change (95% CI)= -0.33 kg (-0.61 to -0.06 kg)] **Authors conclusion** We identified no difference in glucose-lowering between insulin glargine and NPH insulin, but less patient reported hypoglycaemia with glargine and slightly less weight gain with NPH in adults with type 2 diabetes.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Mean net changes, CI 7. CI not wide

Evidence Table : **Effectiveness**

Question : **Is long-acting insulin analogues (insulin glargine) effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	17. Mu P, Lu H, Zhang G, Yanning C, Fu J, Wang M, Shu J, Zeng L. Comparison of fasting capillary glucose variability between glargine and NPH. Diabetes Research and Clinical Practice.2011:e4-e7
Study Type / Methods	Randomised controlled trial (RCT) in China The objective of this study was to investigate the glycaemic variability between insulin glargine and NPH Type 2 diabetes mellitus (DM) patients were randomly assigned into two groups for basal insulin therapy at bedtime: insulin glargine or human NPH insulin. Patients were selected based on inclusion and exclusion criteria. The doses of insulin were titrated to attain the goal which was defined as fasting blood glucose (FBG < 6.0 mmol/L). The regimens were maintained for 3 months after the target was reached.
LE	II-I
Number of patients & Patient characteristics	A total of 260 adults with type 2 diabetes mellitus were included:- - 130 treated with glargine - 130 treated with NPH insulin Baseline characteristics were similar between two groups:- • Insulin glargine group [Mean± SD)]:- - Age = 40.3 ± 8.5 - Diabetes duration (years) = 4.9 ± 2.6 - HbA1c (%) = 9.82 % ± 1.56 - FPG (mmol/L) = 10.21 ± 2.82 - 2 h PPG (mmol/L) =16.2 ± 4.33 - CV-FBG (%) =13.4 ± 3.6 - 44.4% male, 55.6% female • NPH insulin group (Mean ± SD):- - Age = 40.6 ± 8.3 - Diabetes duration (years) = 4.7 ± 2.4 - HbA1c (%) = 9.68 % ± 1.73 - FPG (mmol/L) = 10.52 ± 2.63 - 2 h PPG (mmol/L) =15.8 ± 3.97 - CV-FBG (%) =9.68 ± 1.73 - 41.3% male, 58.7% female
Intervention	Insulin glargine
Comparison	NPH insulin
Length of follow up (if applicable)	3 months

Outcome measures/ Effect size	Overall, a total of 250 patients [124 (95.3%) in the insulin glargine group and 126 (96.9%) in the NPH insulin group] completed the study:-
	
	 - Patients withdrawal was the reason for study discontinuation
	
	 At the end of the study:-
	
	 a. Glycaemic control (baseline to endpoint change)
	
	 • HbA1c (Mean ± SD):-
	
	   - Insulin glargine group (6.52 % ± 1.34%)
	
	   - Insulin NPH group (7.63 % ± 1.18%),
	
	   - Mean difference between IGlar and NPH, p < 0.05)
	
	 • Fasting Plasma Glucose (Mean ± SD):-
	
	   - Insulin glargine group (5.50 mmol/L ± 0.22 mmol/L)
	
	   - Insulin NPH group (5.42 mmol/L ± 0.26 mmol/L)
	
	   - Mean difference between IGlar and NPH, p > 0.05)
	
	 • 2 hour Post Prandial Glucose (Mean ± SD):-
	
	   - Insulin glargine group (7.71 mmol/L ± 0.52 mmmol/L)
	
	   - Insulin NPH group (8.26 mmol/L ± 0.63 mmol/L)
	
	   - Mean difference between IGlar and NPH, p < 0.05
	
	 • Coefficient of variation (CV)- FBG (Mean ± SD):-
	
	   - Insulin glargine group (10.2 % ± 4.2%)
	
	   - Insulin NPH group (19.6 % ± 6.1%),
	
	   - Mean difference between IGlar and NPH, p < 0.05
	
	 Authors conclusion
	
	 Our results demonstrated that insulin glargine was more potent in improving glycaemic control than NPH with stable fasting blood glucose and without increasing hypoglycaemia in inadequately controlled Type 2 DM with oral anti diabetics alone.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Effectiveness**

Question : **Is long-acting insulin analogues (insulin glargine) effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	18. Mattia GD, Laurenti O, Moretti A. Comparison of glycaemic control in patients with type 2 diabetes on basal insulin and fixed combination of oral antidiabetic treatment: results of a pilot study. Acta Diabetol.2009; 46:67-73
Study Type / Methods	Randomised controlled trial (RCT) in Italy The aim of this study was to determine either by CGMS or by venous plasma glucose excursion measurement the relative impact of isulin glargine and NPH insulin on FBG and postprandial glucose handling after a mixed meal in patients with type 2 diabetes mellitus Randomised, controlled, open-label, national, single centre, two- way cross -over study. The study comprised a 1-week run-in-phase, followed by two 12-week treatment phases and 2-week safety follow-up phase. At visit 2 (baseline) patients were randomised to either Sequence A (glargine followed by NPH insulin) or sequence B (NPH insulin followed by insulin glargine). Study drugs were cross-over after 12 weeks of treatment.
LE	II-I
Number of patients & Patient characteristics	A total of 21 patients with type 2 diabetes mellitus were included of whom 10 were assigned to Sequence A and 11 were assigned to Sequence B Baseline characteristics of patients Mean ± SD):- - Age (years) = 59. ± 8.2 - 70% male, 30% female - HbA1c (%) = 9.3 % ± 1.4 - Weight (kg) = 82.7 ± 8.7 - BMI (kg/m^2) = 29.5 ± 2.0 - Fasting blood glucose (mg/dL)= 203.6 ± 58.3
Intervention	Insulin glargine plus OADs
Comparison	NPH insulin plus OADs
Length of follow up (if applicable)	27 weeks

Outcome measures/ Effect size	20 patients (95.2%) completed the total study period. One patient assigned to sequence A discontinued the study at visit 2 owing to consent withdrawal.
	
	At the end of the study:-
	
	a. Glycaemic control (baseline to endpoint change)
	
	• Both insulin provided similar improvements in glycaemic control:-
	
	• HbA1c (Mean ± SD):-
	
	  - Insulin glargine group = (-1.7 % ± 1.6%, P <0.0001)
	
	  - Insulin NPH group = (-1.6 %± 1.6%, P <0.001)
	
	• Mean amplitude of glucose excursions (MAGE) index (Mean and 95% CI):-
	
	  - Insulin glargine group = [-17.0 mg/dL (-34.5 to 0.6 mg/dL, P= 0.058)]
	
	  - Insulin NPH group = [-13.1 mg/dL(-31.4 to 5.3mg/dL, P= 0.152)]
	
	  - Mean difference between the two treatment = P = 0.603
	
	• Mean daily blood glucose (MDBG), Mean ± 95% CI:-
	
	  - Insulin glargine group = [-40.9 mg/dL (-57.0 to -24.8 mg/dL, P< 0.0001)]
	
	  - Insulin NPH group = [-43.9 mg/dL (-59.9 to -27.8 mg/dL, P< 0.0001)]
	
	  - Mean difference between the two treatment = P=0.701
	
	b. Meal test
	
	Post prandial blood glucose was significantly lower after a standard meal test performed at 13:00 h the day after insulin injection with insulin glargine versus NPH (P=0.02)
	
	c. Insulin dose
	
	• Total daily dose at end point:-
	
	  - Insulin glargine group, 28.8 Unit
	
	  - NPH insulin group, 34.7 Unit
	
	Authors conclusion
	
	Adding insulin glargine to existing OADs is more effective in reducing postprandial blood glucose fluctuations during the day compared with NPH insulin plus OADs, with lower incidence of hypoglycaemia.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

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Evidence Table : **Effectiveness**

Question : **Is long-acting insulin analogues (insulin detemir) effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	19. Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S, Jones RH, Umpleby A, Russel-Jones D. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care. 2011;34:1487-1491
Study Type / Methods	Randomised controlled trial (RCT) in United Kingdom The objective of this study was to investigate whether this effect was a result of reduced energy intake and/or increased energy expenditure A randomised, single centre, open-labelled, cross over design trial was undertaken in 23 patients with type 1 diabetes. Patients on a basal-bolus regimen (with insulin aspart as the bolus insulin) were randomly assigned to insulin detemir or NPH insulin as a basal insulin for 16 weeks, followed by the other basal insulin for 16 weeks. At the end of the of each 16 weeks period, total energy expenditure, energy intake, weight change, glycaemic control, hypoglycaemic episodes, and hormones that affect safety and fuel partitioning were measured. During the trial, subjects attended the hospital for eight planned visits, and the investigator was in contact with the patients by telephone at least 10 times.
LE	II-I
Number of patients & Patient characteristics	A total of 23 patients with type 1 diabetes mellitus were included in the study. - Male to female ratio; 14 to 9 - Average age (mean $\pm$ SE) = 38.8 $\pm$ 2.17 years - Average weight (mean $\pm$ SE) = 81.9 $\pm$ 2.21 kg - BMI (mean $\pm$ SE) = 28 $\pm$ 3.6 kg/m^2 - Duration of diabetes (mean $\pm$ SE) = 19.95 $\pm$ 2.09 years - HbA1c (mean $\pm$ SE) = 8.2 $\pm$ 0.22%
Intervention	Insulin detemir
Comparison	NPH insulin
Length of follow up (if applicable)	32 weeks

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Outcome measures/ Effect size (Con't)	Overall, a total of 22 patients (95.6%) completed the study:-
	
	- One patient did not complete the trial for personal reasons
	
	After 16 weeks of treatment
	
	a. Body weight
	• Weight change (Mean ± SE):-
	  - Insulin detemir group (-0.69 kg ± 0.39 kg)
	  - NPH insulin group (1.7 kg ± 0.52 kg)
	  - (P<0.001)
	
	• Fat mass change (Mean ± SE):-
	  - Insulin detemir group (0.16 kg ± 0.45 kg)
	  - NPH insulin group (0.42 kg ± 0.38 kg)
	  - (P=0.562)
	
	• Fat-free mass change (Mean ± SE):-
	  - Insulin detemir group (-0.9 kg ± 0.25 kg)
	  - NPH insulin group (1.26 kg ± 0.31 kg)
	  - (P<0.001)
	
	b. Energy intake and expenditure
	
	• Energy intake (Mean ± SE):-
	  - Insulin detemir group (2,018 kcal/day ± 109.4 kcal/day)
	  - NPH insulin group (2,181 kcal/day ± 122.1 kcal/day, (P=0.026)
	  (This was attributed to lower fat (P=0.006) and protein (P=0.001)
	
	• Total energy expenditure (Mean ± SE):-
	  - Insulin detemir group (3,074 kcal/day ± 301.5 kcal/day)
	  - NPH insulin group (3,233 kcal/day ± 236)
	
	c. Glycaemic control
	• HbA1c (Mean ± SE):-
	  - Insulin detemir group (7.8 % ± 0.23%)
	  - NPH insulin group (7.5 % ± 0.26%)
	  - (P=0.061)
	
	Authors conclusion
	The reduced weight gain with the insulin detemir compared with NPH insulin is attributed to reduced energy intake rather than increased energy expenditure. This may be mediated by a direct or indirect effect of insulin detemir on the hormones that control satiety.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table	**: Effectiveness**
Question	**: Is long-acting insulin analogue (insulin detemir) effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	20. Szypowska A, Golicki D, Groele L, Pankowska E. Long-acting insulin analogue determir compared with NPH insulin in type 1 diabetes. A systematic review and meta-analysis. Polskie Archiwum Medycyny Wewnetrznej. 2011;121(7-8): 237-245.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to compare the effect of treatment with detemir insulin versus NPH insulin in metabolic control, hypoglycaemic episodes, and body weight gain in patients with type 1 diabetes Electronic databases were systematically searched; MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Database of Systematic Reviews for randomised clinical trials on humans up to November 2010.Reference lists from original studies and review articles were screened. The Novo Nordisk trial register was searched for unpublished trials. No restrictions in language. Data extraction was performed independently by two reviewers. The duration of studies at least 12 weeks. The quality of studies that met the inclusion criteria was assessed independently by reviewers without blinding to authorship or journal. Comprehensive Meta-analysis ver. 2 software was used.
LE	I
Number of patients & Patient characteristics	10 studies met the inclusion criteria:- • 7 full-text articles • 3 unpublished trials • 3,825 patients with type 1 　- 3,048 adults 　- 777 children • All trials contained sufficient proportion (≥ 80%) of participants in the final analysis. • Duration of intervention ranged from 4 to 24 months. • 9 parallel-group design, one was crossover study. • All studies were open-label, as detemir and NPH are visually distinguishable and patients self-administered insulin.
Intervention	Long-acting insulin analogue (Insulin Detemir)
Comparison	[Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Type 1 DM (Insulin detemir versus NPH):-** **a. HbA1c** • **(10 trials, 3,758 patients)** [WMD (95% CI)= -0.073% (-0.135 to -0.011%, P=0.021)] I^2=0.00% **b. Fasting plasma glucose (FPG)** • **(10 trials, 3,748 patients):-** [WMD (95% CI) = -0.977 mmol/L (-1.395 to -0.558 mmol/L, P<0.001)] I^2=66.5% **c. Body weight** • **(6 trials, 3,096 patients)** [WMD (95% CI)= -0.779 kg (-0.992 to -0.567kg, P<0.001)] I^2=0.00% **Authors conclusion** We identified no difference in glucose-lowering between insulin glargine and NPH insulin, but less patient reported hypoglycaemia with glargine and slightly less weight gain with NPH in adults with type 2 diabetes.
General comments	Quality assessment (CASP) 1. Yes　2. Yes　3. Yes　4. Yes　5. Yes　6. WMD, CI and P value　7. CI not wide

Evidence Table : Effectiveness

Question : Is long-acting insulin analogues (insulin detemir) effective for treatment of type 1 diabetes mellitus compared to human insulin?

Bibliographic citation	21. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. Pediatric Diabetes.2011;12: 632-641
Study Type / Methods	Randomised controlled trial (RCT) in India The objective of this study was to compare the efficacy and safety of treatment with insulin detemir (IDet) and neutral protamine Hagedorn (NPH) insulin in this vulnerable age group (2 to 5 years) after 52 weeks of treatment. 52-weeks, multinational, open-labelled, randomised (IDet: NPH) two-armed parallel group trial involving 82 children aged between 2 and 5 years, recruited from diabetes clinics at 32 sites in 10 countries. Both treatment groups received insulin aspart as bolus insulin with main meals and large snacks. The trail consisted of a 2-weeks screening period, followed by a 52-weeks titration and treatment period, including a total of 10 scheduled visits to the clinical trial sites and 8 telephone contacts. Eligible subjects were allocated to treatment with IDet or NPH in a 1:1 ratio and randomisation was carried out using a centralised telephone and web-based randomisation system, the Interactive Voice Response System (IVRS), and performed within 2 weeks after screening visit. Since IDet and NPH were easily distinguishable by visual inspection, and as the primary end-point, HbA1c was not easily biased, an open-labelled study design was chosen.
LE	II-I

Number of patients & Patient characteristics	A total of 82 children with type 1 diabetes mellitus were included:-
	
	- 42 treated with IDet
	
	- 40 treated with NPH
	
	Baseline characteristics were similar between two groups:-
	• IDet group [Mean (SD)]:-
	  - Age = 4.3 (1.2)
	  - Diabetes duration (yr) = 2.2 (1.0)
	  - HbA1c (%) = 8.2 (4.9%)
	  - FPG (mmol/L) = 8.4 (4.9)
	  - 57.1% female, 42.9% male
	
	• NPH group (Mean ± SD):-
	  - Age = 4.5 (1.0)
	  - Diabetes duration (yr) = 2.1 (0.8)
	  - HbA1c (%) = 8.1 (1.2)
	  - FPG (mmol/L) = 8.6 (4.1)
	  - 47.5% female, 52.5% male

Intervention	Iinsulin detemir (IDet)
Comparison	Neutral protamine Hagedorn (NPH)
Length of follow up (if applicable)	52 weeks

Outcome measures/ Effect size	41 (97.6%) subjects in the IDet and 39 (97.5%%) in the NPH group completed the study:-
	
	- One child withdrew from the IDet group due to adverse events and one child withdrew from the NPH group due to ineffective therapy.
	
	a. Glycaemic control
	
	• Mean HbA1c:-
	  - IDet (8.2 % at baseline versus 8.1% at 1 year)
	  - NPH (8.1 % at baseline versus 8.3% at 1 year
	
	• Mean Fasting Plasma Glucose:-
	  - Decreased in both groups from baseline to end of trial but effects greater in those receiving IDet
	  - [IDet (-1.0 mmol/L) versus NPH (-0.45 mmol/L)]
	
	• 9 point self measured plasma glucose (SMPG):-
	  - Decreased and become flattened during the trial
	  - More subjects in the IDet group (47.6%) than in the NPH group (35.0%) reached pre breakfast plasma glucose target (4.0 to 7.0 mmol/L) during the trial
	
	b. Mean standard deviation (SD) score of body weight:-
	• Change in observed mean weight SD score standardised by age and gender was -0.17 with IDet and 0.03 with NPH
	
	Authors conclusion
	Long term treatment with IDet in children aged 2 to 5 years suggested similar glycaemic control, greater reduction in fasting plasma glucose, lower rates of hypoglycaemia, no inappropriate weight gain, and fewer adverse events compared with NPH.

General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

Evidence Table **: Effectiveness**

Question **: Is long-acting insulin analogues effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	22. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues Versus NPH human insulin in type 1diabetes: A meta-analysis. Diabetes, Obesity and Metabolism. 2009;11:237-245.
Study Type / Methods	Systematic Review and meta-analysis The objective of this meta-analysis was to assess the differences with respect to HbA1c, incidence of hypoglycaemia, and weight gain between NPH human insulin and each long-acting analogue in type 1 diabetes mellitus. An extensive Medline search for detemir and glargine was performed, collecting all clinical trials on humans up to 1 April 20008. Unpublished trials were also searched. Identification, selection and data extraction was performed independently by two reviewers. The duration of studies at least 12 weeks. The quality of studies was assessed using Jadad scale. Comprehensive Meta-analysis ver. 2 software was used.
LE	I
Number of patients & Patient characteristics	20 trials included in the meta-analysis • 3,693 patients in insulin analogues group and 2,485 patients in the NPH group • Duration of intervention ranged from 12 to 52 weeks. • 18 parallel-series design • 18 were sponsored trials
Intervention	Long-acting insulin analogue (Insulin Detemir and Insulin Glargine)
Comparison	[Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM :-**
	
	a. HbA1c
	• **Overall (Insulin detemir and Insulin glargine versus NPH)**
	  [Standardised Mean Difference (95% CI)= -0.07% (-0.13 to -0.011%, P=0.026)]
	
	b. Body weight
	• **Insulin determir versus NPH (8 trials)**
	  [Standardised Mean Difference (95% CI)= 0.26 kg/m^2 (0.06 to 0.47 kg/m^2), P<0.012)]
	
	Authors conclusion
	The switch from NPH to long-acting analogues as basal insulin replacement in type 1 diabetic patients had a small effect on HbA1c, and also reduced the risk of nocturnal and severe hypoglycaemia.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Standar-dised Mean Difference, CI and P value 7. CI not wide

Evidence Table   : **Effectiveness**

Question   : **Is long-acting insulin analogues (insulin detemir) effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	23. Fajardo Montanana C, Hernandez Herrero C, Rivas Fernandez M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients-The PREDICTIVE™ BMI clinical trial. Diabet. Med.2008;25:916-923
Study Type / Methods	Randomised controlled trial (RCT) in Spain The objective of this study was to assess weight change when once-daily insulin detemir or neutral protamine Hagedorn insulin (NPH) are used in already overweight type 2 diabetes patients requiring intensifies insulin therapy A 26-week, parallel-group, randomised, controlled treat-to-target trial comparing once-daily detemir and NPH insulin in intensive insulin regimens in obese or overweight subjects with type 2 diabetes in 41 centres in Spain between September 2005 and December 2006. The trial was open-label because detemir and NPH insulin can be easily distinguished visually. At screening, subjects were randomised to receive one daily bedtime injection of either detemir or NPH insulin at approximately the same of the day, plus insulin aspart three times daily at main meals. Randomisation was stratified by centre, with each participating centre receiving sufficient sealed codes, in blocks of six. Local investigators enrolled patients and assigned them to groups by choosing the lowest available randomisation number at their site; treatment was then revealed by scratching off the protective surface of the sealed code. After randomisation, subjects made five further visits to the clinic, with the last visit at 26 weeks, and had telephone contacts between visits, 2,4 and 5. Each centre was required to use the same weighing scale throughout the trial. Statistical analyses of efficacy and safety were based on intention to treat population (all randomised subjects exposed to at least one dose of trial product)
LE	II-I

Number of patients & Patient characteristics	A total of 277 patients were randomised to treatment.
	- 126 treated with insulin detemir
	- 151 treated with NPH
	
	Baseline characteristics of patients were well matched except the NPH group contained more patients.
	
	• Insulin detemir group [Mean± SD)]:-
	  - Age = 62.1 ± 9.3
	  - Diabetes duration (years) = 16.2 ± 8.7
	  - HbA1c (%) = 8.9 % ± 0.9
	  - FPG (mmol/L) = 10.8 ± 3.5
	  - 37.6% male, 62.4% female
	  - Weight (kg) = 79.5 ± 11.9
	  - Body mass Index (kg/m^2) = 31.6 ± 4.3
	
	• NPH insulin group (Mean ± SD):-
	  - Age = 61.8 ± 8.3
	  - Diabetes duration (years) = 16.4 ± 7.4
	  - HbA1c (%) = 8.8 % ± 1.0
	  - FPG (mmol/L) = 10.1 ± 3.6
	  - 43.2% male, 56.8% female
	  - Weight (kg) = 82.2 ± 12.2
	  - Body mass Index (kg/m^2) = 32.0 ± 4.2

Intervention	Insulin detemir
Comparison	NPH Insulin
Length of follow up (if applicable)	26 weeks

Outcome measures/ Effect size	Overall, a total of 258 patients (93.1%) completed the study:-
	
	- 119 (94.4%) in the detemir group and 139 (92.0%) in the NPH group
	
	- In the detemir group, one withdrew due to adverse event, three due to non-compliance and three because of other reasons
	
	- In the NPH group, two withdrew due to adverse event, two due to ineffective therapy, two due to non-compliance and five because of other reasons
	
	Intention to treat analysis:-
	
	- (n) =125 in the detemir group
	
	- (n) =146 in the NPH group
	
	After 26 weeks of treatment
	
	a. Body weight
	
	• Weight change (Mean BMI increased):-
	
	  - Insulin detemir group (0.2 kg/m^2)
	
	  - NPH insulin group (0.8 kg/m^2)
	
	  - Baseline-adjusted between treatment difference = 0.6 kg/m^2 (P<0.0001)
	
	• Overall, 46.4% of detemir patients showed no change or lost weight, compared with 22.6% of NPH insulin patients
	
	b. Glycaemic control
	
	• HbA1c (Mean ± SD):-
	  - Insulin detemir group
	    decreased from 8.9 % ± 0.9% to 7.8 % ± 1.1%
	    NPH insulin group from 8.8 % ± 1.0% to 7.8 ± 1.0%
	
	• FPG (Mean ± SD):-
	  - Insulin detemir group
	    decreased from 10.8 % ± 3.5% to 8.8 % ± 2.7%
	    NPH insulin group from 10.1 % ± 3.6% to 8.9 ± 3.1%
	  - Between treatment differences in glycaemic control were not significant.
	
	Authors conclusion
	
	Use of once-daily detemir for intensification of insulin therapy resulted in less weight gain, less hypoglycaemia and equivalent glycaemic control compared with NPH.

General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

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Evidence Table	**: Effectiveness**
Question	**: Is Premixed Insulin analogues effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	24. Qayyum R, Wilson LM, Bolen S, Maruthur N, Marinopoulus SS, Feldman L, Ranasinghe P, Amer M, Bass EB. Comparative effectiveness, safety, and indications of insulin analogues in premixed formulations for adults with type 2 diabetes. Comparative Effectiveness Review No. 14. (Prepared by the John Hopkins University Evidence-based Practice Center). AHRQ Publication No. 08-EHC017-EF, 2008
Study Type / Methods	Systematic Review and meta-analysis

The objective of this review was to assess the effectiveness and safety of all premixed insulin analogues that are approved by the U.S. Food and Drug Administration (FDA) and available in the United States.

The following databases were searched: MEDLINE (1966 to February 2008), EMBASE (1974 to February 2008), the Cochrane Central Register of Controlled Trials (CENTRAL;1966 to February 2008), CINAHL (1982 through February 2008). Hand-searched 13 journals. Also reviewed the reference lists of included studies.

Two independent reviewers selected trials for inclusion. Each article underwent double review by study investigators, at the level of data abstraction and assessment of study quality. The second reviewer confirmed the first reviewer's data abstraction form for completeness and accuracy.

A quality assessment tool was developed for randomised controlled trails and non randomised studies based on Jadad criteria and the Newcastle-Ottawa Scale.

Meta-analyses for outcomes were conducted when there were sufficient data (two or more trials) and studies were homogenous. |
| **LE** | I |
| **Number of patients & Patient characteristics** | A total of 45 studies, represented in 50 articles were included:-

• 16 studies compared premixed insulin analogues with premixed human insulin

• 2 studies compared premixed insulin analogues with intermediate acting human insulin |
Intervention	Premix insulin analogues (insulin aspart 70/30, insulin lispro 75/25, insulin lispro 50/50)
Comparison	Premixed human insulin (NPH/regular 70/30, NPH/regular 50/50) or NPH insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**a. Fasting glucose**

• **Insulin aspart 70/30 versus premixed human insulin preparations:-**

 Pooled mean difference and 95% confidence interval (CI)=8.33 mg/dL (0.16 to 16.49 mg/dL; P=0.04) I^2=23.0%

• **Insulin lispro 75/25 versus premixed human insulin preparations:-**

 Pooled mean difference and 95% confidence interval (CI)=0.12 mg/dL (-6.05 to 6.29 mg/dL; P=0.97) I^2=0.0%

• **Insulin lispro 50/50 versus premixed human insulin preparations:-**

 - Insulin lispro 50/50 may be less effective than premixed human insulin

 - Effect size in two studies

  (1) mean difference=30.3 mg/dL, P<0.0001

  (2) mean difference=23 mg/dL,   P=non significant |

Outcome measures/ Effect size	**b. Postprandial glucose**
	
	• **Insulin aspart 70/30 versus premixed human insulin preparations:-**
	Pooled mean difference and 95% confidence interval (CI)= -18.56 mg/dL (-31.15 to -5.97 mg/dL; P=0.004) I^2=26.0%
	
	• **Insulin lispro 75/25 versus premixed human insulin preparations:-**
	Pooled mean difference and 95% confidence interval (CI)= -17.83 mg/dL (-27.02 mg/dL to -8.65 mg/dL; P<0.001) I^2=0.0%
	
	• **Insulin lispro 50/50 versus premixed human insulin preparations:-**
	Pooled mean difference and 95% confidence interval (CI)= -30.3 mg/dL (-55.6 mg/dL to -5.0 mg/dL; P=0.02)
	
	c. HbA1c
	
	• **Insulin aspart 70/30 versus premixed human insulin preparations:-**
	Pooled mean absolute difference and 95% confidence interval (CI)=0.06% (-0.04 to 0.16%; P=0.22) I^2=0.0%
	
	• **Insulin lispro 75/25 versus premixed human insulin preparations:-**
	Absolute mean difference reported in three studies ranged from -0.12% to 0.2%, P was not significant.
	
	• **Insulin lispro 50/50 versus premixed human insulin preparations:-**
	
	- Insulin lispro 50/50 may be less effective than premixed human insulin
	
	- Effect size in two studies
	
	  (1) Absolute mean difference = -0.5%, P=0.01
	
	  (2) Absolute mean difference = -0.31%, P<0.05

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Mean Difference, 95% CI, P value 7. CI is wide INAHTA checklist for HTA report

Evidence Table	**: Effectiveness**
Question	**: Is premixed insulin analogues effective for treatment of type 1 or type 2 diabetes mellitus compared to premixed human insulin?**

Bibliographic citation	25. Gao Y, Li G, Guo X, Yuan G, Gong Q, Yan L, Zhen Y, Zhang J. Postprandial blood glucose response to a standard test meal in insulin –requiring patients with diabetes treated with insulin lisro mix 50 or human insulin mix 50. Int J Clin Pract. 2008;62(9):1344-1351
Study Type / Methods	Randomised controlled trial (RCT) in China. The aim of this study was to compare the 2-hour postprandial blood glucose (PPBG) excursion following a standard meal in insulin-requiring patients with diabetes treated twice daily with human insulin mix 50 versus lispro mix 50 (LM50). A multicentre (three centres in China), randomised, open-label, 2 sequence, 2 period, cross-over trial in patients with type 1 or type 2 diabetes treated twice daily with human insulin mix 50 versus LM50. Standard test meals were administered to compare these insulin treatments for their effect on 2-hour PPBG excursion. Patients were randomised to two groups in a 1:1 ratio, with 60 patients in each sequence group. One sequence group received twice-daily treatment with LM50, followed by 12 weeks of twice daily treatment with human insulin mix 50 (Sequence 1). The other group received the reverse treatment of the sequence 1. Diabetic retinopathy status was assessed in seven-field stereoscopic fundus photographs obtained at screening and after 3, 6, 12, 24, 36, 48 and 60 months of treatment. Photographs underwent treatment-group-masked grading without comparison with other photographs. To verify progression status, a side-by-side comparison of baseline and follow-up photographs masked to treatment was conducted by a senior grader for any patient whose ETDRS score demonstrated a three step or greater progression over baseline at any time point during the study.
LE	II-I
Number of patients & Patient characteristics	A total of 120 adults with type 1 and type 2 diabetes mellitus were included, 60 patients in each sequence group:- Baseline characteristics were generally similar between two groups (according to sequence):- • Sequence group 1 [Mean± SD)]:- - Age (years) = 54.3 ± 10.1 - 37.0% male, 63.0% female - Diabetes duration (years) = 10.7 ± 6.9 - HbA1c (%) = 8.41 % ± 1.38 - Weight (kg) = 100.2 ± 22.7 - Duration of prior treatment with insulin (years) = 5.5 ± 6.6 - Moderate NPDR or worse (level 43/<43 or worse) = 53 ± 10.3 • Sequence group 2 (Mean ± SD):- - Age (years) = 57.2 ± 8.6 - 53.6% male, 46.4% female - Diabetes duration (years) = 10.8 ±6.7 - HbA1c (%) = 8.31% ±1.38 - Weight (kg) = 98.7 ± 22.3 - Duration of prior treatment with insulin (years) = 4.9 ± 5.1 - Moderate NPDR or worse (level 43/<43 or worse) = 53 ± 10.3
Intervention	Lispro mix 50 (LM50)
Comparison	Human insulin mix 50
Length of follow up (if applicable)	24 weeks

Outcome measures/ Effect size	Overall, a total of 115 patients completed the study [57 (93.4%) in sequence 1 and 58 (96.7%) in sequence 2 completed the study
	
	At the end of the study:-
	
	a. Mean 2-hour postprandial blood glucose excursion
	
	• LM50 group:-
	
	  - decreased from 6.32 ± 3.07 mmol/L at baseline to 3.47 ± 3.00 mmol/L at end-point (reduction of 2.89 ± 3.27 mmol/L)
	
	• Human insulin mix group group:-
	
	  - decreased from 6.31 ± 2.88 mmol/L at baseline to 5.02 ± 3.32 mmol/L at end-point (reduction of 1.32 ± 3387 mmol/L)
	
	  - decreased greater with LM50 when compared with human insulin mix 50 (P <0.001)
	
	b. Blood glucose:-
	
	- Mean fasting blood glucose was higher in patients with LM50 than in those on human insulin mix 50 (P = 0.023)
	
	- 2-hour PPBG (P=0.004) and 1-hour PPBG excursion (P< 0.001) were lower with LM50 than with human insulin mix.
	
	c. HbA1c:-
	
	- The two treatments provided equivalent mean HbA1c values (P=0.581) and mean change from baseline HbA1c values (P=0.456) at treatment end-points.
	
	- Mean HbA1c was 7.59% (decreased by 0.48%) from baseline with LM50 and was 7.61% (decreased 0.46% from baseline) with human insulin mix.
	
	d. Insulin dose requirement:-
	
	- Were similar in both treatment groups, at each visit and end-point, for morning, evening and total doses.
	
	Authors conclusion
	
	Insulin lispro mix 50 provided better postprandial glycaemic control compared with human insulin mix 50 while providing the convenience of injecting immediately before meals. Both treatments were generally well tolerated by all randomly assigned patients.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

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Evidence Table   **: Effectiveness**

Question   **: Is premixed insulin analogues effective for treatment of type 1 or type 2 diabetes mellitus compared to premixed human insulin?**

Bibliographic citation	26. Li Y, Li Q, Li C, Wang C, Zheng Y, Maher I, Zhang J. Comparison of HbA1c in Chinese patients with type 1 or type 2 diabetes randomized to twice daily insulin lispro low mix 25 or twice daily human insulin mix 30/70. Chin Med J. 2009; 122(21):2540-2546
Study Type / Methods	Randomised controlled trial (RCT) in China. The aim of this study was demonstrate that twice daily insulin lispro low mix 25 is non inferior to twice daily human insulin mix 30/70 in achieveing glycaemic control as measured by HbA1c, from baseline to endpoint, in patients with type 1 or 2 3 diabetes. In this phase 1V, crossover, open-label, multicenter study, 117 Chinese patients with diabetes were randomly assigned to one of the two treatment sequence groups. One group received 12-week treatment with twice daily human insulin mix 30/70 followed by 12-week treatment with twice daily insulin lispro low mix 25, while the other group received the reverse treatment sequence. HbA1c, baseline-to-endpoint change in HbA1c, proportion of patients achieved target HbA1c $\leq$ 7% and $\leq$ 6.5%, fasting blood glucose, and daily insulin doses were measured for each period. Safety and tolerability were also assessed.
LE	II-I

Number of patients & Patient characteristics	A total of 117 patients with type 1 and type 2 diabetes mellitus were included:-
	
	- 57 patients in sequence group 1
	
	- 60 patients in sequence group 2
	
	Baseline characteristics according to sequence:-
	
	• Sequence group 1 [Mean (SD)]:-
	  - Age (years) = 54 (10.8)
	  - 45.6% male, 54.4% female
	  - Diabetes duration (months) = 130 (95.6)
	  - HbA1c (%) = 8.6 (1.3)
	  - Weight (kg) = 67 (12.2)
	  - Duration of prior treatment with insulin (months) = 39 (37.4)
	
	• Sequence group 2 (Mean $\pm$ SD):-
	  - Age (years)= 55 $\pm$ 10.8
	  - 41.7% male, 58.3% female
	  - Diabetes duration (months) = 130 (78.3)
	  - HbA1c (%) = 8.6% (1.6)
	  - Weight (kg) = 64 (9.6)
	  - Duration of prior treatment with insulin (months) = 39 (32.4)

Intervention	Insulin lispro low mix 25 (25% insulin lispro, 75% insulin protamine suspension) (LM50)
Comparison	Human insulin mix 30/70 (30% human insulin/70% NPH)
Length of follow up (if applicable)	24 weeks
Outcome measures/ Effect size	Overall, a total of 113 patients completed the study [54 (94.7%) in sequence 1 and 59 (98.3%) in sequence 2 completed the study **At the end of the study (12 weeks):-** **a. HbA1c:-** - A statistically significant reduction (P ≤ 0.0001) was achieved after each treatment; human insulin mix 30/70 (mean HbA1c =7.91%, 95% CI: 7.67 to 8.15%); insulin lispro mix 25 (mean HbA1c =7.96%, 95% CI: 7.72 to 8.20%) - Adjusted mean difference between the two treatments after 12 weeks was -0.05% (95% CI; -0.20 to 0.10%) - No statistically significant difference noted for HbA1c ≤ 7.0% target (P= 0.644) and the HbA1c ≤ 6.5% (P= 0.672) between the two treatments. **b. Fasting blood glucose (FBG)** - No statistically significant difference (P= 0.4190) in change from baseline to endpoint FBG was observed between the two treatments, with mean reduction in FBG of 1.04 mmol/L (95% CI; 0.57 mmol/L to 1.51 mmol/L) observed for human insulin mix and mean reduction of 1.18 mmol/L (95% CI; 0.71 mmol/L to 1.65 mmol/L) for insulin lispro mix. **Authors conclusion** The results support non inferiority of twice daily insulin lispro low mix 25 versus twice daily human insulin mix 30/70 in HbA1c control in Chinese patients with type 1 or type 2 diabetes.
General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table	**: Effectiveness**
Question	**: Is premixed insulin analogues (BiAspart 30) effective for treatment of diabetes mellitus in pregnant women compared to premixed human insulin?**

Bibliographic citation	27. Balaji V, Balaji MS, Alexander C, Ashalata S, Suganti RS, Suresh S, Seshiah V. Premixed Insulin Aspart 30 (BIAsp 300 vs Premixed Human Insulin 30 (BHI 30) in Gestational Diabetes Mellitus-A Pilot Project. JAPI. 2010;58:95-97
Study Type / Methods	Randomised controlled trial (RCT) in India The objective of this study was to compare premixed insulin aspart 30 (BIAsp 30) versus premixed human insulin 30 (BHI 30) on efficacy, safety, foetal and perinatal outcomes in pregnancies associated with gestational diabetes mellitus (GDM). 152 GDM women were randomly assigned to receive either BIASp 30 or BHI 30. GDM women in Group A were initiated on 6 units of BIASp 30 before breakfast and similarly Group B women on the same dose of 6 units BHI 30. They were instructed on self monitoring of blood glucose (SMBG) using Accucheck active and to attend antenatal clinic for routine check up monthly. Also asked to record hypoglycaemic episodes and adverse events.
LE	II-I

Number of patients & Patient characteristics	A total of 152 GDM were included:-
	 - 76 treated with BIASp 30
	 - 76 treated with BHI 30
	
	 Baseline characteristics:- no significant difference between the two groups; P>0.05
	 • BIAsp 30 group (Mean ± SD):-
	    - Age = 28.92 ± 3.59
	    - Body mass index; = 27.18 ± 3.87 kg/m^2
	    - Gestational weeks at entry=22.75 ± 8.83
	    - Fasting plasma glucose (mg/dl) = 102.97 ± 18.67
	    - HbA1c (%) =6.10 ± 0.45
	
	 • BHI 30 group (Mean ± SD):-
	    - Age = 29.38 ± 4.64
	    - Body mass index; = 26.34 ± 4.02 kg/m^2
	    - Gestational weeks at entry=22.64± 9.23
	    - Fasting plasma glucose (mg/dl) = 103.58 ± 20.25
	    - HbA1c (%) =6.12 ± 0.72

Intervention	Premixed insulin analogues (BIAsp 30)
Comparison	Premixed human insulin BHI 30
Length of follow up (if applicable)	From 22nd week of pregnancy untill confinement

Outcome measures/ Effect size	There was 100% compliance and follow-up data was available for all 152 subjects.
	
	 a. Glycaemic control (HbA1c before confinement):-
	
	 • Mean ± SD :-
	    - BIAsp 30 (5.98 %± 0.52% mmol/L)
	    - BHI 30 (6.04 %± 0.61%), P>0.05
	
	 b. Insulin requirement (IU/L):-
	 • Mean ± SD :-
	    - BIAsp 30 IU/L (17.20 ± 18.66 IU/L)
	    - BHI 30 IU/L (20.55 ± 20.92 IU/L) P>0.05
	
	 Authors conclusion
	 IAsp was safe during pregnancy and pregnant women found it convenient due to meal time dosing. Foetal outcome using BIAsp 30 was also comparable with BHI 30.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table	**: Safety**
Question	**: Is short-acting insulin analogues safe for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	1. Barnajee S, Tran K, Li H, Cimon K, Daneman D, Simpson S, Campbell K. Short-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness. Technology report No 87. Ottawa: Canadian Agency for drugs and Technologies in Health, 2007.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to evaluate the clinical and economic implications of short-acting insulin analogues [insulin Lispro (ILis), insulin aspart (IAsp), and insulin glulisine (IGlu)] for the treatment of type 1, type 2, and gestational diabetes mellitus (DM). Electronic searches of the MEDLINE, BIOSIS Previews, PASCAL and EMBASE databases were searched from 1990 until January 2006 with no language restrictions. Parallel search was run on PubMed and Cochrane databases. Last Cochrane updates were performed on February 6, 2006. Grey literature was also searched. Two reviewers independently selected trials for inclusion. Data from each included trial were extracted by two of three individuals working independently and using a structured form. The quality of the included RCTs was evaluated using the Jadad five-point scale. Cochrane software Review Manager 4.2.3 was used to analyse data and generate forest plots. If $I^2 >75\%$ the studies were not pooled. When hypoglycaemia was expressed as an episode rate, the WMD was calculated, and when hypoglycaemia was expressed in terms of number of patients having episode(s), the RR was calculated. A review of economic studies and budget impact analysis were performed
LE	I
Number of patients & Patient characteristics	A total of 86 RCTs were included:- • 47 on type 1 DM • 26 on type 2 DM • 10 on Type 1 and 2 combined • 3 on gestational DM Most of the studies were of low methodological quality (Jaded score ≤ 2) RCTs on type 1 DM:- • Number of patients in the trials varied between 10 and 1,070 • 8 involved paediatric population (mean age ranged between 8 and 15 years) • 39 involved mainly adults (mean age ranged 23 to 48 years) • 29 cross over trials and 18 parallel trials • 31 mentioned industry sponsorship RCTs on type 2 DM:- • Number of patients in the trials varied between 21 and 876 • 25 reported mean age (between 54 and 68 years) • 7 cross over trials and 20 parallel trials • 19 mentioned industry sponsorship RCTs on type 1 and type 2 DM • Mean age ranged between 32 and 64 years • Number of females varied between 28% to 59% RCTs on gestational DM • 2 journal articles and one conference abstract • 1 mentioned industry sponsorship • All compared ILis with HI • Two reported mean age ranging between 30 and 35 years
Intervention	Short-acting insulin analogues (ILis, IAsp, or IGlu)
Comparison	Conventional human insulin (HI) or oral antidiabetic drugs (OADs)

Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM:-**
	
	a. Hypoglycaemia
	
	• **ILis versus HI**
	
	    Overall hypoglycaemia (all, 19 trials, 5,795 patients):-
	    Results not pooled, I^2=93.1%16 trials reported no significant difference in the overall rate of hypoglycaemia between ILis and HI.
	
	    Severe or major hypoglycaemia (16 trials, 2,543 patients):-
	    [RR (95% CI)= 0.77 (0.47 to 1.27)] I^2=0.0%
	
	    Nocturnal hypoglycaemia (all, 4 trials, 1,377 patients):-
	    [WMD (95% CI)= -0.55 (-0.92 to -0.19)] I^2=56.0%
	
	• **IAsp versus HI (14 trials):-**
	    Patients in the IAsp and HI groups had the same incidence rate for overall, severe, and nocturnal hypoglycaemia.
	
	• **IGlu versus HI (1 trial):-**
	    No significant differences between treatments for symptomatic and nocturnal hypoglycaemia.
	    Non significant higher rate of severe hypoglycaemia in the HI group.
	
	Type 2 DM:-
	
	a. Hypoglycaemia
	
	• **ILis (or IlisMix) versus HI (or HIMix)**
	
	    Overall hypoglycaemia (7 trials, 2,762):-
	    [WMD (95% CI)= -0.16 (-0.39 to 0.07)] I^2=0.0%
	
	    Overall hypoglycaemia (3 trials, 384):-
	    [RR (95% CI)=1.24 (0.90 to 1.71)] I^2=0.0%
	
	    Severe hypoglycaemia (2 trials, 1,622 patients):-
	    [RR (95% CI)=0.43 (0.08 to 2.37)] I^2=0.0%
	
	    Nocturnal hypoglycaemia (2 trials, 1,570 patients):-
	    [WMD (95% CI)= -0.24 (-0.39 to -0.08)] I^2=0.0%
	
	    Nocturnal hypoglycaemia (1 trial, 178 patients):-
	    [RR (95% CI)=1.63 (0.71 to 3.73)]
	
	• **IAsp versus HI (5 trials, 987 patients):-**
	    No significant difference for overall, severe, and nocturnal hypoglycaemia.
	
	• **IGlu versus HI (5 trials, 4,220 patients):-**
	    No significant differences between treatments for overall, severe, and nocturnal hypoglycaemia.
	
	b. Adverse events
	
	• Of 49 reports on type 1 DM, 26 did not report on adverse events.
	
	• Of 24 reports on Type 2 DM, 6 did not report on adverse events.
	    - Adverse events included headache, pharyngitis, rhinitis, upper respiratory infection, flu syndrome, pain and injection site reactions.
	    - Most were judged to be unrelated to treatment. No difference between treatments with HI or short-acting insulin analogues.
	
	Authors conclusion
	
	For type 1 DM, the episodes of overall and severe hypoglycaemia were similar, but nocturnal hypoglycaemia was less frequent with ILis than with HI. For type 2 DM, short-acting insulin analogues did not result in significant reductions in hypoglycaemic episodes. Uncertainty remains regarding the use of short-acting insulin analogues in gestational DM patients and pregnant women with diabetes.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, RR, 95% CI 7. CI is not wide INAHTA checklist for HTA report

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Evidence Table	**: Safety**
Question	**: Is insulin analogues safe for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	2. Singh SR, Ahmad F, Lal A, Yu C, Bai Z, Bennet H. Efficacy and safety of insulin analogues for the management of diabetes mellitus; a meta-analysis. CMAJ.2009;180(4):285-297
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to compare the outcome of insulin analogues with conventional insulins in the treatment of type1, type 2 and gestational diabetes. Two earlier systematic reviews of the efficacy and safety of rapid-and long-acting insulin analogues (Barnajee *et al.* and Tran *et al.*, CADTH, 2007) were updated. Original search strategy used for the health technology assessments were updated to include studies published up to April 2007. Electronic searches of the MEDLINE (1966 to April 2007), MEDLINE In-Process and Other Non-Indexed Citations, MEDLINE Daily Update, EMBASE (1980 to April 2007), BIOSIS Previews (1989 to April 2007) and the Cochrane Library (Issue 3, 2007). Limited the search to randomised controlled trials. Grey literature was also searched. Studies selected based on inclusion criteria. Two reviewers independently assessed the methodological quality of the included studies of rapid-acting insulin analogues and another two reviewers assessed the included studies of long-acting analogues using Jadad scale. Each of the reviewers independently extracted data from the articles included in the analysis using a predesigned form. Data extraction at the study level was repeated for studies contained in the two original health technology assessments. Data were combined using random-effects model. An $I^2 \geq 50\%$ represent moderate heterogeneity and $I^2 \geq 75\%$ represent high level of heterogeneity.
LE	I
Number of patients & Patient characteristics	Rapid-acting insulin analogues:- • Selected 5 trials (total =68 RCTs for meta-analysis) Long-acting insulin analogues:- • Selected 20 and one trial was identified by stakeholders (total=49 RCTs for meta-analysis). • Most of the trials included were multinational and sponsored by industry. • Trial duration ranged from 4 weeks to 30 months. • Number of patients in each study ranged from 7 to 1,008. • Of the 48 crossover studies, most lacked or did not mention a washout period. • All studies were of open-label design. • Most trials was rated as poor (Jaded score 2 or 3) • No major differences across trials in terms of patients characteristics (e.g. sex, degree of obesity, and severity or duration of diabetes).
Intervention	Rapid-acting or Long-acting insulin analogues
Comparison	Conventional human insulin (HI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM:-**
	
	a. Hypoglycaemia (adult)
	
	(rapid-acting insulin analogues)
	• **Insulin lispro versus regular human insulin (severe hypoglycaemia, 10 trials, 4,502 patients):-**
	  [RR (95% CI)= 0.80 (0.67 to 0.96)] I^2=0.0%
	• **Insulin lispro versus regular human insulin (nocturnal hypoglycaemia, 4 trials, 725 patients):-**
	  [RR (95% CI)= 0.51 (0.42 to 0.62)] I^2=73.1%
	• **Insulin aspart versus regular human insulin (severe hypoglycaemia, 4 trials, 1,814 patients):-**
	  [RR (95% CI)= 0.83 (0.65 to 1.04)] I^2=0.0%
	• **Insulin aspart versus regular human insulin (nocturnal hypoglycaemia, 1 trials, 118 patients):-**
	  [RR (95% CI)= 0.55 (0.43 to 0.70)] I^2= NA

	(long-acting insulin analogues)
	• **Insulin glargine versus NPH insulin (severe hypoglycaemia, 7 trials, 2,227 patients):-** [RR (95% CI)= 0.82 (0.52 to 1.29)] I^2= 33.0%
	• **Insulin glargine versus NPH insulin (nocturnal hypoglycaemia, 5 trials, 1,943 patients):-** [RR (95% CI)= 0.97 (0.87 to 1.09)] I^2= 65.6%
	• **Insulin detemir versus NPH insulin (severe hypoglycaemia, 7 trials, 2,442 patients):-** [RR (95% CI)= 0.74 (0.58 to 0.96)] I^2= 0.0%
	• **Insulin detemir versus NPH insulin (nocturnal hypoglycaemia, 6 trials, 2,311 patients):-** [RR (95% CI)= 0.92 (0.85 to 0.98)] I^2= 32.2%
	b. Hypoglycaemia (children and adolescents)
	(rapid-acting insulin analogues)
	• **Insulin lispro versus regular human insulin** **(children, severe hypoglycaemia, 3 trials, 222 patients):-** [RR (95% CI)= 0.69 (0.24 to 2.01)] I^2= 0.0%
	• **Insulin lispro versus regular human insulin** **(children, nocturnal hypoglycaemia, multiple daily injections only, 3 trials, 234 patients):-** [RR (95% CI)= 0.96 (0.74 to 1.26)] I^2= 0.0%
	• **Insulin lispro versus regular human insulin** **(adolescents, severe hypoglycaemia, multiple daily injections only, 1 trial, 926 patients):-** [RR (95% CI)= 1.00 (0.29 to 3.43)] I^2= NA%
	• **Insulin lispro versus regular human insulin** **(adolescents, nocturnal hypoglycaemia, multiple daily injections only, 1 trial, 926 patients):-** [RR (95% CI)= 0.61 (0.57 to 0.64)] I^2=NA%
Outcome measures/ **Effect size (Con't)**	**(long-acting insulin analogues)**
	• **Insulin glargine versus NPH insulin or insulin lente** **(children and adolescents, severe hypoglycaemia, 4 trials, 727 patients):-** [RR (95% CI)= 1.18 (0.59 to 2.35)] I^2=48.0%
	• **Insulin glargine versus NPH insulin or insulin lente** **(children and adolescents, nocturnal hypoglycaemia, 1 trial, 349 patients):-** [RR (95% CI)= 0.71 (0.43 to 1.18)] I^2=NA
	• **Insulin detemir versus NPH insulin** **(children and adolescents, severe hypoglycaemia, 1 trial, 347 patients):-** [RR (95% CI)= 0.80 (0.50 to 1.28)] I^2=NA
	• **Insulin detemir versus NPH insulin** **(children and adolescents, nocturnal hypoglycaemia, 1 trial, 347 patients):-** [RR (95% CI)= 0.85 (0.77 to 0.94)] I^2=NA
	Type 2 DM:-
	a. Hypoglycaemia (adult)
	(rapid-acting insulin analogues)
	• **Insulin lispro versus regular human insulin (severe hypoglycaemia, 2 trials, 1,622 patients):-** [RR (95% CI)= 0.43 (0.08 to 2.37)] I^2=0.0%
	• **Insulin lispro versus regular human insulin (nocturnal hypoglycaemia, 1 trial, 178 patients):-** [RR (95% CI)= 1.63 (0.71 to 3.73)] I^2=NA
	• **Insulin aspart versus regular human insulin (severe hypoglycaemia, 1 trial, 121 patients):-** [RR (95% CI)= 0.39 (0.11 to 1.36)] I^2=NA
	• **Insulin aspart versus regular human insulin (nocturnal hypoglycaemia, 1 trial, 93 patients):-** [RR (95% CI)= 0.65 (0.28 to 1.53)] I^2=NA
	(long-acting insulin analogues)
	• **Insulin glargine versus NPH insulin** **(with oral antidiabetic therapy in both groups, severe hypoglycaemia, 7 trials, 2,866 patients):-** [RR (95% CI)= 0.66 (0.29 to 1.48)] I^2= 64.3%
	• **Insulin glargine versus NPH insulin** **(with oral antidiabetic therapy in both groups, nocturnal hypoglycaemia, 7 trials, 2,532 patients):-** [RR (95% CI)= 0.56 (0.47 to 0.68)] I^2= 32.3%

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Outcome measures/ Effect size (Con't)	• **Insulin glargine versus NPH insulin** **(without oral antidiabetic therapy, nocturnal hypoglycaemia, 1 trial, 518 patients):-** [RR (95% CI)= 0.78 (0.62 to 0.98)] I²= NA • **Insulin detemir versus NPH insulin** **(with oral antidiabetic therapy in both groups, severe hypoglycaemia, 2 trials, 808 patients):-** [RR (95% CI)= 0.75 (0.03 to 20.0)1] I²= 68.8% • **Insulin detemir versus NPH insulin** **(with oral antidiabetic therapy in both groups, nocturnal hypoglycaemia, 2 trials, 808 patients):-** [RR (95% CI)= 0.53 (0.31 to 0.91)] I²= 51.6% • **Insulin detemir + insulin aspart versus NPH insulin + regular human insulin** **(severe, 1 trial, 394 patients):-** [RR (95% CI)= 1.02 (0.26 to 4.02)] I²= NA • **Insulin detemir + insulin aspart versus NPH insulin + regular human insulin** **(nocturnal, 1 trial, 394 patients):-** [RR (95% CI)= 0.54 (0.3 to 0.97)] I²= NA **Adverse events** • The most commonly reported adverse events were infections of the upper respiratory tract, reactions at the injection site and weight gain. • The incidence of adverse events was similar between insulin analogues and conventional insulin. • Serious adverse events were uncommon. **Authors conclusion:** Rapid- and long-acting insulin analogues offer little benefit relative to conventional insulin in terms of glycaemic control and reduced hypoglycaemia. Long-term, high quality studies are needed to determine whether insulin analogues reduce the risk of long-term complications of diabetes.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. RR or rate ratio 95% CI 7. CI is not wide

Evidence Table : **Safety**

Question : **Is short-acting insulin analogues (insulin lispro) safe for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	3. Brunetti P, Muggeo M, Cattin L, Arcangeli A, Pozzilli P, Provenzano V, Francesconi A, Calatola P, Santeusanio F. Incidence of severe nocturnal hypoglycaemia in patients with type 1 diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. Nutrition, Metabolism & Cardiovascular Diseases. 2010;20:519-526
Study Type / Methods	Randomised controlled trial (RCT) in Italy The objective of this study was to further investigate the pairing of insulin glargine with either RHI or lispro in Type 1 diabetes mellitus (DM) National, multicentre, randomised, parallel-group, open label, non-inferiority, Phase III trial. The study duration was 28 weeks including a 2-week running period, 8-week qualification phase, 16-week treatment phase and 2-week follow-up. Patients from hospitals or diabetes clinics were recruited through the referral of diabetologists who manage patients with type 1 DM in Italy. At the end of the qualification phase, patients were randomised (V4) in accordance with the randomisation sequence. The randomisation sequence was generated by the study biometrician and the investigators were not blinded to the randomisation list. Patients continued to receive insulin glargine at dinner time and were randomised to either regular human insulin (RHI) or lispro at each meal time
LE	II-I

Number of patients & Patient characteristics	A total of 395 adults with type 1 diabetes mellitus were included:-
	
	- 202 treated with glargine and RHI
	
	- 193 treated with glargine and insulin lispro
	
	Baseline characteristics were similar between two groups:-
	• Insulin glargine and RHI group [Mean± SD)]:-
	
	  - Age = 35.2 ± 10.5
	
	  - Diabetes duration (years) = 13.0 ± 8.8
	
	  - HbA1c (%) = 7.39 % ± 0.88
	
	  - FPG (mmol/L) = 10.4 ± 3.1
	
	  - 57.9% male, 42.1% female
	
	• Insulin glargine and insulin lispro group (Mean ± SD):-
	
	  - Age = 35.3 ± 9.9
	
	  - Diabetes duration (years) = 13.0 ± 8.8
	
	  - HbA1c (%) = 7.39 % ± 0.97
	
	  - FPG (mmol/L) = 10.1 ± 2.8
	
	  - 64.8% male, 35.2% female

Intervention	Insulin glargine and lispro
Comparison	Insulin glargine and RHI
Length of follow up (if applicable)	28 weeks
Outcome measures/ Effect size	Overall, a total of 373 patients [192 (95.0%) in the RHI group and 181 (93.7%) in the lispro group] completed the study:- - Consent withdrawal was the main reason for early study discontinuation **a. Hypoglycaemia** • **Severe nocturnal hypoglycaemia:-** - proportion of patients experiencing severe hypoglycaemia at the end of the study was three (1.55%) in the RHI group versus 2 (1.11%) in the lispro group, P=0.938 - Mean difference was 0.44% (95% CI: -1.77 to 2.21%) - Overall incidence 0.015 versus 0.016 episodes /patient/month for the RHI and lisro group respectively, P= 0.924 • **Overall hypoglycaemia:-** - No difference in the incidence of overall hypoglycaemia between the two groups (2.85 versus 2.85 episodes / patient / month, respectively) **Authors conclusion** The results from this study suggest that insulin glargine in combination with short-acting analog or RHI was associated with similar and low rate of nocturnal hypoglycaemia and glycaemic control, owing to the peakless once-daily evening insulin glargine injection in both arms.
General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

Evidence Table	**: Safety**
Question	**: Is short-acting insulin analogues (insulin aspart) safe for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	4. Rys P, Pankiewicz O, Lach K, Kwaskowski A, Skrzekowska-Baran I, Malecki MT. Efficacy and safety comparison of rapid-acting insulin aspart and regular human insulin in the treatment of type 1 and type 2 diabetes mellitus: A systematic review. Diabetes & Metabolism. 2011;37:190-200
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to compare outcomes of treatment with insulin aspart (IAsp) and regular human insulin (RHI), as well as biphasic insulin aspart (BIAsp) and and biphasic human insulin preparations (BHI) in type 1 and type 2 diabetes mellitus patients. The MEDLINE, EMBASE, CENTRAL, and Centre for Reviews and Dissemination was systematically searched. The final search was carried out in July 2009. References listed in the retrieved articles were also used. Two reviewers independently identified the relevant abstracts and selected studies according to the criteria and extracted the data for analysis. The selection criteria include randomised controlled trials with an intervention duration of at least four weeks. The quality of RCTs was also assessed, using the parameters proposed by Jadad *et al.* Dichotomous data were pooled using relative risk (RR). Meta-analysis for continuous endpoints were expressed as weighted mean difference (WMD) or standardized mean difference (SMD). If, clinical trials were heterogenous (P<0.01), their results were pooled using a random-effects model.
LE	I
Number of patients & Patient characteristics	A total of 28 trials were included:- • 18 for type 1 DM • 11 for type 2 DM Type 1 DM:- • 14 involved adult patients • 4 included children and/or adolescents • 13 studies were RCTs with parallel design • 5 studies were RCTs with crossover design. • Only two studies were double blind • Allocation concealment was provided in three of the 18 studies • Mean HbA1c ranged from 6.9% to 9.6% Type 2 DM:- • 6 studies were RCTs with parallel design • 5 studies were RCTs with crossover design. • Only two studies were double blind • Allocation concealment was provided in one of the 11 studies • 11 trials included adult patients • Mean HbA1c ranged from 7.3% to 9.8% • Mean baseline BMI was between 28 kg/m^2 and 32 kg/m^2

Intervention	Insulin aspart (IAsp) or biphasic insulin aspart (BIAsp)
Comparison	Regular human insulin (RHI) or biphasic human insulin (BHI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM:-**
	
	a. All hypoglycaemic episodes
	• **(6 studies, 2,220):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [1.06 (1.01 to 1.10)] I^2= NA
	
	b. Nocturnal hypoglycaemic episodes
	• **(3 studies, 2,065):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [0.67 (0.54 to 0.83)] I^2= NA
	
	c. Severe hypoglycaemic episodes
	• **(7 studies, 2,358):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [0.92 (0.75 to 1.12)] I^2= NA
	
	Type 2 DM:-
	
	a. All hypoglycaemic episodes
	• **(5 studies, 882):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [1.04 (0.92 to 1.17)] I^2= NA
	
	b. Nocturnal hypoglycaemic episodes
	• **(1 study, 93):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [0.65 (0.28 to 1.48)] I^2= NA
	
	c. Severe hypoglycaemic episodes
	• **(2 studies, 206):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [0.67 (0.17 to 2.53)] I^2= NA
	
	Authors conclusion:
	Analysis based on a systematic review showed that treatment with IAsp in type 1 DM patients resulted in moderately better metabolic control and treatment satisfaction than RHI. In type 2 DM patients, meta-analysis showed improvement in post prandial glucose, but not in other outcomes.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. RR, 95% CI 7. CI is not wide

Evidence Table **: Safety**

Question **: Is short-acting insulin analogues (insulin aspart) safe for treatment of diabetes mellitus in pregnant women compared to human insulin?**

Bibliographic citation	5. Mathiesen ER, Kinsley B, Amiel B, Ameil SA, Heller S, McCancre D, Duran S, Bellaire S, Raben A. Maternal glycemic control and hypoglycaemia in type 1 diabetic pregnancy. A randomized trial of insulin aspart versus human insulin in 322 pregnant women. Diabetes Care. 2007;30 (4):771-776
Study Type / Methods	Randomised controlled trial (RCT) The objective of this study was to assess the safety and efficacy of insulin aspart (IAsp) versus regular human insulin (HI) in basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes. Subjects who were either pregnant with singleton pregnancy (gestational age ≤ 10 weeks) or planning to become pregnant were randomised (1:1) to IAsp or HI in combination with NPH insulin one to four times per day in an open-label, parallel-group study conducted at 63 sites in 18 countries, mainly within Europe. Because study insulin injection timing varied, an open-label approach was used. Subjects had AIC ≤8% at confirmation of pregnancy. Subjects not pregnant at screening were withdrawn if not pregnant ≤12 months after randomisation. Insulin doses were titrated toward predefined glucose targets and AIC <6.5%. Subjects were recruited between September 2002 and August 2004; the last follow-up visit was in April 2005. In total, 412 subjects were randomised and treated. Of these 322 (IAsp, 157; HI, 165) were pregnant during the study. Outcome assessed included risk of major maternal hypoglycaemia, AIC, plasma glucose profiles , and maternal safety outcomes. Treatment satisfaction was assessed using the Diabetes Treatment Satisfaction Questionnaire at randomisation and at follow-up visits. Subjects ranked 8 items on a 7-point Likert scale to measure overall treatment satisfaction (satisfaction with treatment, flexibility, diabetes understanding, convenience, and willingness to continue treatment and recommend treatment). Higher scale = greater treatment satisfaction.
LE	II-I
Number of patients & Patient characteristics	A total of 322 were included:- - 157 treated with insulin aspart - 165 treated with HI Baseline characteristics • IAsp group (Mean ± SD) or n (%):- - Age = 29.0 ± 4.7 - Body mass index; 24.9 ± 4.0 kg/m^2 - Duration of diabetes (years) = 12.2 ± 7.1 - AIC (%) =7.0 ± 0.8 - Retinopathy = 43 (27.4%) - Neuropathy = 7 (4.5%) HI group (Mean ± SD) :- - Age = 29.0 ± 4.5 - Body mass index; 24.6 ± 3.7 kg/m^2 - Duration of diabetes (years) = 11.8 ± 7.4 - AIC (%) =6.9 ± 1.0 - Retinopathy = 45 (27.3%) - Neuropathy = 4 (2.4%)
Intervention	Short-acting insulin analogues (insulin aspart)
Comparison	Regular human insulin
Length of follow up (if applicable)	Maximum duration of participation was 22 months

Outcome measures/ Effect size	264 (81.98%) completed pregnancy and the trial intervention:-
	
	- Of the 58 non completers (IAsp, 24; HI, 34) 31 were withdrawn due to adverse events (IAsp, 14; HI, 17)
	
	- 27 for other reasons (IAsp, 10; HI, 17)
	
	a. Hypoglycaemic episodes
	
	Major maternal hypoglycaemia
	(requiring third party assistance with plasma glucose <3.1 mmol/L: or reversal of symptoms after food, glucagon, or intravenous glucose)-
	
	• **(IAsp versus HI):-**
	  1.4 episodes/year exposure versus 2.1 episodes / year exposure
	  Relative risk (RR) and 95% confidence interval (CI) = [0.72 (0.36 to 1.46)] P= not significant (NS)
	
	Major nocturnal maternal hypoglycaemia:-
	• **(IAsp versus HI):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [0.48 (0.20 to 1.14] P= not significant (NS)
	
	Major daytime maternal hypoglycaemia:-
	• **(IAsp versus HI):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [0.85 (0.40 to 1.78] P= not significant (NS)
	
	Any nocturnal maternal hypoglycaemia:-
	• **(IAsp versus HI):-**
	  Relative risk (RR) and 95% confidence interval (CI) = [0.76 (0.57 to 1.03] P= not significant (NS)
	
	b. Adverse events
	
	• No maternal deaths were reported
	
	• Both insulins were well tolerated and the adverse event profiles were similar
	
	• Most events were mild or moderate and considered unlikely to be related to the study products
	
	• 18 serious adverse events were considered to have a possible relation to the study medication (caesarean section (IAsp, 2; HI, 0), abortion (IAsp, 2; HI, 0), hypoglycaemic coma (IAsp, 2; HI, 5), investigator-defined inadequate glycaemic control (IAsp, 2; HI, 4), and hyperglycaemia (IAsp, 0; HI, 3).
	
	• 31 subjects left the study because of adverse events (IAsp, 14; HI, 17).
	
	c. Diabetes complications
	
	• No clinically significant difference in deterioration in fundoscopy was reported in either treatment group.
	
	Authors conclusion
	
	IAsp is at least as safe and effective as HI when used in basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes and may potentially offer some benefits in terms of postprandial glucose control and preventing severe hypoglycaemia.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

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Evidence Table : **Safety**

Question : **Is short-acting insulin analogues (insulin aspart) safe for treatment of diabetes mellitus in pregnant women compared to human insulin?**

Bibliographic citation	6. Pettitt DJ, Ospina P, Howard C, Zisser H, Jovanoic L. Efficacy, safety and lack of immunogenecity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. Diabet. Med. 2007;324:1129-1135
Study Type / Methods	Randomised controlled trial (RCT) The objective of this study was to assess the efficacy and safety of insulin aspart (IAsp) compared with regular human insulin (HI) as a bolus component of basal-bolus therapy for subjects with gestational diabetes mellitus (GDM). In this single-centre, randomised, parallel group, open-label trial, 27 women with GDM were randomised to receive either IAsp, 5 minutes before meal or regular human insulin. The trial period extended from diagnosis of insulin requiring GDM (18 to 28th week of pregnancy) to 6 weeks postpartum.
LE	II-I

Number of patients & Patient characteristics	A total of 27 women were included:-
	- 14 treated with insulin aspart
	- 13 treated with HI
	
	Baseline characteristics
	• IAsp group (Mean ± SD):-
	  - Age = 31.6 ± 5.9
	  - Body mass index; 24.3 ± 4.7 kg/m^2
	  - HbA1c (%) =5.1 ± 0.4
	
	• HI group (Mean ± SD) :-
	  - Age = 29.7 ± 6.9
	  - Body mass index; 33.2 ± 5.7 kg/m^2
	  - HbA1c (%) =5.3 ± 0.3

Intervention	Short-acting insulin analogues (insulin aspart)
Comparison	Regular human insulin
Length of follow up (if applicable)	From 18 to 28th week of pregnancy to 6 weeks postpartum

Outcome measures/ Effect size	13 (93%) subjects in the IAsp and 9 (69%) in the HI group completed the study:-
	- Four subjects discontinued the study since they delivered early and one subject discontinued the study due to the inability during the meal test to provide adequate blood samples because of excessive clotting.
	
	a. Adverse events (AEs):-
	• 14 subjects reported a total of 27 adverse events
	  - 8 (57%) subjects with 16 AEs in IAsp group
	  - 6 (46%) subjects with 11 AEs in the HI group
	• In both treatments groups the most frequently reported AEs was upper respiratory tract infections.
	• The investigators considered fatigue (1 subject) and somnolence (1 subject) and injection site reactions (IAsp, 1 subject and HI, 2 subjects) to be the only AEs possibly/probably related to the study drug.
	
	b. Hypoglycaemic episodes:-
	• Symptomatic hypoglycaemic episodes reported by 19 subjects (10 in IAsp group and 9 in the HI group)
	• No hypoglycaemic episodes required assistance of another person
	
	c. Pregnancy outcome
	• Determined by neonatal assessment (weight, length, physical examination findings) were similar in both treatment groups.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Safety**

Question : **Is short-acting insulin analogues (insulin aspart) safe for treatment of diabetes mellitus in pregnant women compared to human insulin?**

Bibliographic citation	7. Hod M, Damm P, Kaaja R, Visser GHA, Dunne F, Demidova I, Hansen AP, Mersebach H. Fetal and perinatal outcomes in type 1 diabetes pregnancy: a randomized study comparing insulin aspart with human insulin in 322 subjects. Am J Obst Gynecol. 2008;198:186.e1-186.e7
Study Type / Methods	Randomised controlled trial (RCT) The objective of this study was to compare insulin aspart (IAsp) with human insulin (HI) in basal-bolus therapy with neutral protamine Hagedorn for foetal and perinatal outcomes of type 1 diabetes in pregnancy. Subjects who were either pregnant with singleton pregnancy (gestational age ≤ 10 weeks) or planning to become pregnant were randomised (1:1) to IAsp or HI in combination with NPH insulin one to four times per day in an open-label, parallel-group study conducted at 63 sites in 18 countries, mainly within Europe. Because study insulin injection timing varied, an open-label approach was used. Subjects had AlC ≤8% at confirmation of pregnancy. Subjects not pregnant at screening were withdrawn if not pregnant ≤12 months after randomisation. Insulin doses were titrated toward predefined glucose targets and AlC <6.5%. Subjects were recruited between September 2002 and August 2004; the last follow-up visit was in April 2005. In total, 412 subjects were randomised and treated. Of these 322 (IAsp, 157; HI, 165) were pregnant during the study. Randomisation was implemented with a block size of 4. At the randomisation visit, the investigator assigned the lowest available subject number at the site and then revealed the assigned treatment by scratching off the protective surface of the sealed code. The statistical analyses of foetal and neonatal safety outcomes were performed on the intention-to-treat pregnant analysis set.
LE	II-I

Number of patients & Patient characteristics	A total of 322 were included:-
	- 157 treated with insulin aspart
	- 165 treated with HI
	
	Baseline characteristics
	• IAsp group- Mean (SD) :-
	  - Age = 29.0 (4.7)
	  - Body mass index; 24.9 (4.0) kg/m^2
	  - Duration of diabetes (years) = 12.2 (7.1)
	  - HbA1c pregnant at screening (%) = 6.8 (0.7)
	  - HbA1c not pregnant at screening (%) = 7.3 (1.0)
	
	• HI group- Mean (SD) :-
	  - Age = 29.0 (4.5)
	  - Body mass index; 24.6 (3.7) kg/m^2
	  - Duration of diabetes (years) = 11.8 (7.4)
	  - HbA1c pregnant at screening (%) = 6.8 (0.8)
	  - HbA1c not pregnant at screening (%) = 7.1 (1.2)

Intervention	Short-acting insulin analogues (insulin aspart)
Comparison	Regular human insulin
Length of follow up (if applicable)	Maximum duration of participation was 22 months

<table>
<tr>
<td>Outcome measures/
Effect size</td>
<td>

264 (81.98%) completed pregnancy and the trial intervention:-

- Of the 58 non completers (IAsp, 24; HI, 34) 31 were withdrawn due to adverse events (IAsp, 14; HI, 17)

- 27 for other reasons (IAsp, 10; HI, 17)

a. Life births and foetal losses

 (IAsp versus HI):-

- 137 live births in the IAsp group and 131 in the HI group

- In the IAsp group:-
  14 foetal losses:-
  - 12 early miscarriages
  - 1 late spontaneous abortion
  - 1 stillbirth

- In the aspart group there was one early neonatal death

- In the HI group:-
  21 foetal losses:-
  - 15 early miscarriages
  - 1 late spontaneous abortion
  - 4 terminations of pregnancy
  - 1 stillbirth

- Perinatal mortality:-
  - 14 per 1000 births in the IAsp versus 22 per 1000 births in the HI

- Preterm delivery:-
  - 28 (20.3%) in the IAsp versus 41 (30.6%) in the HI, P= 0.05

- Mean birth weight:-
  - 3438 gram in the IAsp versus 3555 g in the HI (P= 0.09)

b. Congenital malformations
- 15 malformations (5.5%) were confirmed:-
  - 6 (4.3%) in IAsp
  - 9 (6.6%) in HI

- The frequency and type of malformations were similar between treatment groups with majority (IAsp, 5: HI, 4) being cardiac related complications

c. Neonatal Hypoglycaemia requiring treatment:-
- Occurred in 98 live births
  - 46 (33.6%) in IAsp
  - 52 (39.7%) with HI treated mothers

Authors conclusion:
The foetal outcome using IAsp was comparable with HI with a tendency toward fewer foetal losses and preterm deliveries.

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<tr>
<td>General comments</td>
<td>

Jadad scale

Randomisation = 2

Blinding = 0

An account of all patients = 1

Total score = 3/5

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</table>

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Evidence Table : **Safety**

Question : **Is short-acting insulin analogues safe for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	8.Siebenhofer A, Plank J, Berghold A, Jeitler K, Horvath K, Narath M, Gfrerer R, Pieber TR. Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus (Review). Cochrane Database of systematic Reviews 2006, Issue 2. Edited (no change to conclusion), published in Issue 1, 2009.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to assess the effects of short acting insulin analogues versus regular human insulin. The Cochrane Library (issue 3, 2005), MEDLINE and EMBASE were searched. Additional searching by using cross-references from original articles, inquiries to pharmaceutical companies and contacted experts and approval agencies. Two reviewers independently selected trials for inclusion. Data from each included trial were extracted by two independent reviewers using data extraction form. The selection criteria include randomised controlled trials with an intervention duration of at least four weeks. Assessment for methodological quality was done using a modification of the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions and the criteria of Schulz and Jadad. Weighted mean differences (WMD) were calculated for the percentage of glycated haemoglobin and random effects model was used for the meta-analysis. Sensitivity analysis was performed.
LE	I

Number of patients & Patient characteristics	A total of 49 RCTs were included:-
	
	• Most of the studies were of poor methodological quality (88%), 12% were of higher quality
	
	• 17 of 42 included RCTs were of parallel design, the others had a crossover design.
	
	• 59% were multi-centres
	
	• Duration of intervention ranged from one to 12 months with mean follow-up of 3.6 months.
	
	• 8,274 participants took part in the 49 RCTs.
	  - 6,184 type 1 diabetic patients
	  - 2,028 type 2 diabetic patients
	  - 107 women with gestational diabetes

Intervention	Short-acting insulin analogues
Comparison	Regular human insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Hypoglycaemia** **a. Overall hypoglycaemic episodes** **Type 1 DM:-** • **(Short acting insulin analogues versus regular human insulin, 10 studies, 4,266 participants):-** Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.23 (-1.14 to 0.69)] I²= 81.0% **Type 2 DM:-** • **(Short acting insulin analogues versus regular human insulin, 5 studies, 2,617 participants):-** Weighted mean difference (WMD) and 95% confidence interval (CI) = [-0.17 (-0.46 to 0.12)] I²= 0.0%

Outcome measures/ Effect size (Con't)	**Children, adolescents, pregnant type 1 diabetic patients, patients with gestational diabetes**
	
	• Overall rate of hypoglycaemic episodes per patient per 30 days-did not significantly differ in prepubertal children
	
	• Hypoglycaemic episodes per patient per 30 days-significantly reduced with insulin analogue (P=0.02) in adolescents
	
	• In pregnant women, event rate regarding biochemical hypoglycaemia was significantly higher in the analogue group compared to the regular group (P<0.05).
	
	• In women with gestational diabetes, the total number of hypoglycaemic events is lower in the lispro group but not significant
	
	b. Incidence of severe hypoglycaemia
	
	Type 1 DM:-
	
	• Ranged from 0 to 247.3 (median 21.8) episodes per 100 person-years for insulin analogies
	
	• Ranged from 0 to 544 (median 46.1) episodes per 100 person-years for regular insulin
	
	Type 2 DM:-
	
	• Ranged from 0 to 30.3 (median 0.3) episodes per 100 person-years for insulin analogies
	
	• Ranged from 0 to 50.4 (median 1.4) episodes per 100 person-years for regular insulin
	
	Children, adolescents, pregnant type 1 diabetic patients, patients with gestational diabetes
	
	• Severe hypoglycaemic episodes-did not significantly differ in prepubertal children and adolescents
	
	• In pregnant women, two patients treated with regular insulin had four episodes of severe hypoglycaemia.
	
	c. Adverse events
	
	• **56% of studies provided information on adverse events**
	
	   - Overall, frequency and type of adverse events are reported to be comparable for the two treatment groups
	
	   - Most of the events were mild in severity, such as respiratory tract infections, headaches, flu symptoms or accidental injuries and were not considered to be related to the investigational medication
	
	   - No statistically significant difference in discontinuation rate was seen between the treatments throughout the trials.
	
	   - Six trials reported on local site reactions and found no difference.
	
	Authors conclusion
	
	Our analysis suggests only minor benefit of short acting insulin analogues in the majority of diabetic patients treated with insulin. Until long term efficacy and safety data are available we suggest a cautious response to the vigorous promotion of insulin analogues.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, 95% CI 7. CI is not wide

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Evidence Table	**: Safety**
Question	**: Is short-acting insulin analogues safe for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	9. Plank J, Siebenhofer A, Berghold A, Jeitler K, Horvath K, Mrak P, Pieber TR. Systematic Review and Meta-analysis of Short-acting Insulin Analogues in patients with Diabetes Mellitus. Arch Intern Med. 2005;165:1337-1344
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to provide information on glucose control, hypoglycaemia, quality of life, and diabetes-specific complications of short acting insulin analogues compared with regular insulin. The Cochrane Library (issue 4, 2003), MEDLINE (January 1966 to December 2003), and EMBASE (January 1974 to December 2003) were searched. Additional searching by using reference lists and abstracts books from major diabetology meetings from 1992 to 2003, contacted three main insulin producing companies and checked bibliographies of textbooks and relevant retrieved articles. Authors and experts were also contacted. Two reviewers independently selected trials for inclusion. Data from each included trial were extracted by two independent reviewers using data extraction form. The selection criteria include randomised controlled trials with an intervention duration of at least four weeks. Assessment for methodological quality was done using a modification of the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions and the criteria of Schulz *et al.* and Jadad *et al.*. Weighted mean differences (WMD) were calculated for the percentage of glycosylated haemoglobin and random effects model was used for the meta-analysis. Sensitivity analysis was performed.
LE	I

Number of patients & Patient characteristics	A total of 42 RCTs were included:-
	
	• 7,933 participants took part in the 42 RCTs:-
	  - 5,925 type 1 diabetes mellitus
	  - 1,901 patients with the type 2 diabetes mellitus
	  - 107 women with gestational diabetes
	
	• Type 1 diabetes mellitus patients:-
	  - Weighted mean age; 46 years
	  - Diabetes duration;14 years
	  - Body mass index; 24.4 kg/m^2
	
	• Type 2 diabetes mellitus patients:-
	  - Weighted mean age; 58 years
	  - Diabetes duration;12 years
	  - Body mass index; 28.2 kg/m^2
	
	• Seven studies were of higher methodological qualities
	
	RCTs included in Meta-analysis
	
	• HbA1c:-
	  - 20 trials with type 1 diabetic patients
	  - 4 trials including type 2 diabetic patients
	
	• Overall hypoglycaemia:-
	  - 9 trials with type 1 diabetic patients
	  - 5 trials including type 2 diabetic patients

Intervention	Short-acting insulin analogues
Comparison	Regular human insulin
Length of follow up (if applicable)	

Outcome measures/ Effect size	Hypoglycaemia **a. Standardized Mean Difference of overall mean hypoglycaemic episodes per patient per month** **Type 1 DM:-** • **(Short acting insulin analogues versus regular human insulin):-** Standardized mean difference (SMD) and 95% confidence interval (CI) = [-0.05 (-0.22 to 0.11)] **Type 2 DM:-** • **(Short acting insulin analogues versus regular human insulin):-** Standardized mean difference (SMD) and 95% confidence interval (CI) = [-0.17 (-0.12 to 0.04)] **b. Overall hypoglycaemic episodes in children, adolescents, pregnant patients with type 1 DM, patients with gestational DM** **Prepubertal children:-** • Overall rate of hypoglycaemic episodes per patient per month did not significantly differ in prepubertal children in either of the studies **Adolescents:-** • Overall rate of hypoglycaemic episodes per patient per month was significantly reduced with insulin analogue group (P<0.02) **Pregnant women:-** • Event rate regarding biochemical hypoglycaemia was significantly higher in the analogue group compared with the regular group (P<0.05) **Gestational diabetes:-** • In one study, the total number of hypoglycaemic events did not differ between groups **c. Pregnancy outcome** • No significant differences in foetal or maternal outcome between patient groups using analogue and regular insulin on pregnant women with type 1 diabetes mellitus and women with gestational diabetes **d. Adverse events** • 60% of studies provided information on adverse events:- - Overall, the reported frequency and type of adverse events (local site reactions, ketoacidosis) and discontinuation rate were comparable for the two treatment groups - Studies were not planned to investigate mortality, effect of insulin analogues on pre-existing late complications, or eventual development of these complications under trial drug treatment
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. SMD, 95% CI 7. CI is not wide

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Evidence Table : **Safety**

Question : **Is long-acting insulin analogues safe for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	10. Tran K, Barnajee S, Li H, Cimon K, Daneman D, Simpson SH, Campbell K. Long-acting insulin analogues for diabetes mellitus: meta-analysis of clinical outcomes and assessment of cost-effectiveness. Technology report No 92. Ottawa: Canadian Agency for drugs and Technologies in Health, 2007.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to evaluate the clinical efficacy and economic implications of long-acting insulin analogues, specifically insulin glargine (IGlar) and insulin determir (IDet), for the treatment of diabetes mellitus (DM). Electronic searches of the MEDLINE, BIOSIS Previews, PASCAL, EMBASE and the Cochrane Database of Systematic Reviews from 1990 until February 2006. Grey literature was also searched. Two of the three reviewers independently selected trials for inclusion. Data from each included trial were extracted by one reviewer using a structured form. Another reviewer checked the data independently. The quality of the included RCTs was evaluated using the Jadad five- point scale. Cochrane software Review Manager 4.2.3 was used to analyse data and generate forest plots. If I^2 >75% the studies were not pooled. The relative risk (RR) and risk difference (RD) of hypoglycaemia were determined using the number of patients who had the condition, for each treatment arm. A review of economic studies and budget impact analysis were performed
LE	I
Number of patients & Patient characteristics	A total of 34 RCTs were included:- • 23 on type 1 DM • 11 on type 2 DM • No RCTS on gestational DM Mean Jadad score with standard deviation (SD) for RCTs reports on type 1 DM was 2.3±0.7 and on type 2 DM was 2.4±0.7. RCTs on type 1 DM:- • Number of patients in the trials varied between 14 and 749 • 1 involved paediatric and young adults (ages from 8 to 21 years) • 2 involved only paediatric (mean age 12 years) • 20 involved adults (mean age between 24 to 43 years) • Mean duration of diabetes ranged between 4.8 and 5.0 years RCTs on type 2 DM:- • mean age (between 53 and 61 years) • mean duration of diabetes between 8.5 and 13.8 years
Intervention	Long-acting insulin analogues (IGar or IDet)
Comparison	Conventional human insulin (HI) or oral antidiabetic drugs (OADs)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM:-**
	
	a. Hypoglycaemia
	• **IGlar versus NPH**
	
	    Overall hypoglycaemia (all, 8 trials, 2,996 patients):-
	    [RR (95% CI)= 1.00 (0.47 to 1.06)] I^2=68.4%
	
	    Severe hypoglycaemia (all, 6 trials, 2,701 patients):-
	    [RR (95% CI)= 0.78 (0.58 to 1.05)] I^2=24.5%, NNT=50
	
	    - **Severe hypoglycaemia (using HI as bolus, 5 trials, 2,082 patients):-**
	      [RR (95% CI)= 0.73 (0.55 to 0.95)] I^2=7.4% NNT was 33
	    - **Severe hypoglycaemia (using ILis as bolus, 1 trial, 619 patients):-**
	      [RR (95% CI)= 1.25 (0.66 to 2.36)]
	
	    Nocturnal hypoglycaemia (all, 7 trials, 2,826 patients):-
	    [RR (95% CI)= 0.92 (0.81 to 1.04)] I^2=70.2%

	• **IDet versus NPH:-**
	Overall hypoglycaemia (all, 7 trials, 2,437 patients):- [RR (95% CI)= 0.99 (0.97 to 1.02)] I²= 19.2%
	Severe hypoglycaemia (all, 8 trials, 2,708 patients):- [RR (95% CI)= 0.75 (0.59 to 0.95)] I²= 0.0% NNT= 50
	- **Severe hypoglycaemia (using IAsp as bolus, 5 trials, 1,554 patients):-** [RR (95% CI)= 0.70 (0.52 to 0.95)] I²= 0.0%
	- **Severe hypoglycaemia (using HI as bolus, 3 trials, 1,154 patients):-** [RR (95% CI)=0.83 (0.56 to 1.22)]
	Nocturnal hypoglycaemia (all, 7 trials, 2,590 patients):- [RR (95% CI)= 0.89 (0.82 to 0.97)] I²=51.2%
	- **Nocturnal hypoglycaemia (using IAsp as bolus, 5 trials, 1,554 patients):-** [RR (95% CI)= 0.84 (0.73 to 0.95)] I2=62.1%
	- **Nocturnal hypoglycaemia (using HI as bolus, 2 trials, 1,036 patients):-** [RR (95% CI)= 0.97 (0.89 to 1.06)] I²=0.0%
	Type 2 DM:-
	a. Hypoglycaemia
	• **IGlar versus NPH**
	Overall hypoglycaemia (all, 6 trials, 2,211 patients):- [RR (95% CI)=0.89 (0.83 to 0.96)] I²=0.0%
	Severe hypoglycaemia (all, 4 trials, 1,885 patients):- [RR (95% CI)=1.09 (0.56 to 2.12)] I²=0.0%
Outcome measures/ Effect size (Con't)	**Nocturnal hypoglycaemia (all, 5 trials, 2,099 patients):-** [RR (95% CI)= 0.57 (0.44 to 0.74)] I²= 56.8%
	- **Nocturnal hypoglycaemia (HI as bolus, 1 trial, 518 patients):-** [RR (95% CI)= 0.78 (0.62 to 0.98)] I²=Not available
	- **Nocturnal hypoglycaemia (OAD as bolus, 4 trials 1,581 patients):-** [RR (95% CI)= 0.52 (0.43 to 0.64)] I²=0.0%
	• **IDet versus NPH** One trial only.
	Overall hypoglycaemia:- [RR (95% CI)=0.91 (0.75 to 1.11)] I²=0.0%
	Nocturnal hypoglycaemia:- [RR (95% CI)=0.66 (0.45 to 0.96)] NNT was 13.
	b. Adverse events
	• Of 23 RCTs on type 1 DM, 16 reported on adverse events.
	• Of 11 RCTs on Type 2 DM, 10 reported on adverse events.
	Adverse events did not seem to be different with the long-acting insulin analogues compared with NPH.
	• Adverse events commonly reported with long-acting insulin analogues were injection site reaction, upper respiratory tract infection, gastrointestinal disorders, neuropathy, oedema, rhinitis, headache, and weight gain.
	• Adverse events that were commonly reported with NPH were injection site reaction, upper respiratory tract infection, gastrointestinal disorders, neuropathy, oedema, rhinitis, headache, and weight gain.
	Authors conclusion
	IGlar reduce the risks of severe hypoglycaemia in type 1 DM patients on bolus HI. IDet reduced the risks of severe and nocturnal hypoglycaemia in type 1 DM patients on bolus IAsp.
	For type 2 DM, pooled analysis suggest that IGlar reduced the risk of overall and nocturnal but not severe hypoglycaemia, while one RCT suggested that IDet can significantly reduce the incidence of nocturnal hypoglycaemia.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, RR, 95% CI 7. CI is not wide INAHTA checklist for HTA report

Evidence Table : **Safety**

Question : **Is long- acting insulin analogue (insulin glargine) safe for treatment of diabetes mellitus compared to human insulin?**

Bibliographic citation	11. Warren W, Weatherly-Jones E, Chilcott J, Beverly C. Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine. Health Technology Assessment 2004;8(45). Health Technology Assessment NHS R&D HTA programme.
Study Type / Methods	Systematic Review The objective of this review was to evaluate the use of insulin glargine in its licensed basal-bolus indication in terms of both clinical and cost-effectiveness. Fourteen electronic bibliographic databases were searched; biological abstracts, CINAHL, Cochrane database, EMBASE, HTA database, MEDLINE, NHS Economic Evaluations Database (NHS EED), OHE Health Economic Evaluation Database, PreMedline, Science Citation Index and Social Sciences Citation Index. No restrictions were applied. Search undertaken until 2002. Data extraction was done by one reviewer. Quality scores for each of the included RCTs were assigned according to the Jadad scale. Length of study was at least 4 weeks.
LE	I

Number of patients & Patient characteristics	13 studies met the inclusion criteria:-
	
	• 8 studies for type 1 DM
	  - 4 full texts
	  - 4 abstracts
	• 5 studies for type 2 DM
	  - 2 full texts
	  - 3 abstracts
	• All were prospective studies, nine were described as RCTs.
	• None of the trials were double blinded, but two compared two formulations of insulin glargine with NPH using partially blinded designs.

Intervention	Long-acting insulin analogues (Insulin Glargine)
Comparison	Other long acting basal insulin [Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	
Outcome measures/ Effect size	Formal meta-analyses of results of studies was not possible as insufficient raw data were available and studies described were of different durations and therefore not directly comparable in terms of their effects on the indices of glycaemic control. **Summary of evidence** • Evidence concerning control of nocturnal hypoglycaemia is equivocal and suggests that where insulin glargine is demonstrated to be superior to NPH, it is when compared with once-daily and not twice-daily NPH. • There is not enough evidence to conclude that insulin glargine is superior to NPH in controlling either symptomatic or severe hypoglycaemia.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Number, % and P value 7. CI not mentioned INAHTA checklist for HTA report

Evidence Table	: Safety
Question	: Is long-acting insulin analogues (insulin glargine) safe for treatment of type 1 diabetes mellitus compared to human insulin?

Bibliographic citation	12. Bolli BG, Songini M, Trovati M, Prato SD, Ghirlanda G, Cordera R, Trevisan R, G Riccardi, Noacco C. Lower fasting blood glucose, glucose variability and nocturnal hypoglycaemia with glargine vs NPH basal insulin in subjects with Type 1 diabetes. Nutrition, Metabolism & Cardiovascular Diseases.2009;19:571-579
Study Type / Methods	Randomised controlled trial (RCT) in Italy The aim of this study was to establish glycaemic control in subjects with type 1 DM treated with basal insulin glargine as compared to NPH. Randomised, parallel group, open-label, multicentre (21 centres), single country study with a 30-week duration (4 week run in phase, 24-week treatment period and 2-week safety assessment). Subjects were randomised during screening to receive either glargine once daily at dinner time or NPH twice (or more) daily (bedtime and lunch) as basal insulin in basal-bolus intensive treatment for type 1 DM patients with insulin lispro as bolus insulin. During the last 2 weeks before the scheduled visit s patients measured BG 2 hour after meals and at 3 a.m., in addition to FBG and pre-prandial BG, to provide 7-point BG profiles to calculate mean daily blood glucose (MDBG) and mean amplitude glucose excursion (MAGE). Participants were to complete the well-being Enquiry for Diabetics (WED) questionnaire at the randomisation visit (week 0) at 12 and at 24 weeks of treatment phase. Episodes of hypoglycaemia and adverse events (AEs) were recorded by the participants in diaries and reported to the investigator at each visit.
LE	II-I

Number of patients & Patient characteristics	A total of 175 adults with type 1 diabetes mellitus were included:-
	- 85 treated with glargine plus insulin lipro
	- 90 treated with NPH insulin plus insulin lispro
	
	Baseline characteristics were similar between two groups:-
	
	• Insulin glargine group [Mean± SD)]:-
	  - Age (years) = 35.5 ± 10.6
	  - 48 male, 37 female
	  - Diabetes duration (years) = 12.9 ± 8.3
	  - HbA1c (%) = 7.8 % ± 0.7
	  - Weight (kg) = 67.5 ± 9.4
	  - Duration of intensive insulin therapy (years) = 8.3 ± 5.6
	
	• NPH insulin group (Mean ± SD):-
	  - Age (years)= 37.0 ± 9.4
	  - 49 male, 41 female
	  - Diabetes duration (years) = 14.8 ± 9.6
	  - HbA1c (%) = 7.8 % ± 0.6
	  - Weight (kg) = 68.4 ± 10.4
	  - Duration of intensive insulin therapy (years) = 9.4 ± 6.5

Intervention	Insulin glargine plus insulin lispro
Comparison	NPH insulin plus insulin lispro
Length of follow up (if applicable)	30 weeks

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Outcome measures/ Effect size	Overall, a total of 152 patients completed the study [78 (91.8%) in the insulin glargine group and 74 (82.2%) in the NPH insulin group] completed the study:-
	
	- In the glargine group, 4 criteria violations, 2 protocol violations and I consent withdrawn were the reasons for discontinuations.
	
	- In the NPH group, 3 criteria violations,3 consent withdrawn, 2 poor compliance, 2 lost to follow-up, 1 protocol violation and I other reason, were the reasons for discontinuations.
	
	At the end of the study:-
	
	a. Hypoglycaemia (baseline to endpoint change)
	
	• Overall hypoglycaemia (Mean ± 95% CI):-
	
	  - Insulin glargine group = [0.26 (-0.84 to 1.35), P = 0.642
	
	  - Insulin NPH group = [0.21 (-0.87 to 1.29), P = 0.698
	
	• Serious hypoglycaemia (Mean ± 95% CI):-
	
	  - Insulin glargine group = [-0.54 (-0.97 to -0.10), P = 0.014
	
	  - Insulin NPH group = [-0.54 (-0.97 to -0.11), P = 0.013
	
	• Serious nocturnal hypoglycaemia (Mean ± 95% CI):-
	
	  - Insulin glargine group = [-0.19 (-0.32 to -0.05), P = 0.006
	
	  - Insulin NPH group = [-0.10 (-0.24 to 0.03), P = 0.123
	
	b. Adverse events (AEs)
	
	• Total number of 52 advers daily:-
	
	  - 27 AEs reported by 19 (22.3%) of patients in the glargine group
	
	  - 25 AEs reported by 13 (15.1%) of patients in the glargine group
	
	  - One patient in each of two groups experienced drug related adverse events (in the glargine group consisted of hypoglycaemia due to error in the glargine administration, while in the NPH group consisted of bilateral micro-aneurysm
	
	  - None of the AEs caused early study discontinuation
	
	Authors conclusion
	
	Switching from NPH to glargine is well tolerated and results into lower FBG, and lower glucose variability while reducing hypoglycaemia.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Safety**

Question : **Is long-acting insulin analogues (insulin glargine) safe for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	13. Chase HP, Arsalanian S, White NH, Tambolane WV. Insulin Glargine versus Intermediate acting insulin as the basal component of multiple daily injection regimes for adolescents with type 1 diabetes mellitus.J Paediatr. 2008;153:547-553
Study Type / Methods	Randomised controlled trial (RCT) in United States The objective of this study was to compare long-acting insulin glargine with intermediate-acting insulin NPH/Lente when used as the basal component of a multiple daily injection (MDM) regimen with prandial insulin lispro in adolescents with type 1 diabetes mellitus (DM) Active-controlled, randomised (1:1) open-label, sex-stratified, 2-arm, parallel-group study. After educational run-in period, patients were randomised to either stay on their existing basal insulin (NPH/Lente insulin twice daily) or to receive the once-daily morning glargine as basal therapy as part of multiple daily injection (MDI) regimen using insulin lispro as the prandial component in both treatment groups. Everyday throughout the treatment period, each patient recorded his or her fasting, preprandial, and bedtime self- monitored blood glucose (SMBG) Study outcome were documented during clinic visit.
LE	II-I

Number of patients & Patient characteristics	A total of 175 adolescents with type 1 diabetes mellitus were included:-
	- 85 treated with glargine plus insulin lipro
	- 90 treated with NPH insulin plus insulin lispro
	
	Baseline characteristics were similar between two groups:-
	
	• Insulin glargine group [Mean (SD)]:-
	  - Age (years) = 13.1(2.4)
	  - 47.4% male, 53.6% female
	  - Diabetes duration (years) = 5.1 (3.4)
	  - HbA1c (%) = 7.8 % (0.8)
	  - Weight (kg) = 57.2 (14.8)
	
	• NPH insulin group (Mean ± SD):-
	  - Age (years)= 13.4 (2.4)
	  - 47.6% male, 52.4% female
	  - Diabetes duration (years) = 5.4 (3.7)
	  - HbA1c (%) = 8.0 % (0.8)
	  - Weight (kg) = 59.1 (18.1)

Intervention	Insulin glargine plus insulin lispro
Comparison	NPH insulin plus insulin lispro
Length of follow up (if applicable)	24 weeks

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Outcome measures/ Effect size	Overall, a total of 157 patients (89.7%) completed the study (per protocol population). [76 (89.4%) in the insulin glargine group and 81 (90.0% in the NPH insulin group] completed the study:- - In the glargine group, one no baseline HbA1c, four treatment duration <148 days, four major protocol violations. - In the NPH group, four no baseline HBA1c, two no post treatment HbA1c, one treatment duration < 148 days and two major protocol violations. **At the end of the study:-** **a. Hypoglycaemia** • The rate of confirmed glucose values <70 mg/dL was higher in patients receiving insulin glargine (P = 0.0298) • No significant difference in the rates of severe hypoglycaemia (P= 0.1814), or occurrence of glucose levels < 50 mg/dL (P= 0.82) or < 36 mg/dL(P= 0.32) **b. Adverse events** • No difference between the two treatment groups in the overall reported incidence of adverse events (P= 0.1944) - 15 patients (17.6%) in the glargine group and 8 patients (8.9%) in NPH/Lente reported possible treatment-emergent adverse events (P= 0.1168). - Metabolism and nutrition disorders (hypoglycaemia, hyperglycaemia, DKA) were the most commonly reported treatment-emergent adverse events (11.8% in insulin glargine versus 5.6% in NPH insulin, P= 0.1803 - Serious adverse events (21.2% in the glargine versus 7.8% in the NPH, P= 0.0164) **Authors conclusion** Insulin glargine is well tolerated in MDI regimens for paediatric patients with type 1 DM and may be more efficacious than NPH/Lente in those with elevated HbA1c
General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table	**: Safety**
Question	**: Is long-acting insulin analogues effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	14.Horvath K, Jeitler K, Berghold A,Horvath K, Ebrahim SH, Gratzer TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes diabetes mellitus (Review). Cochrane Database of systematic Reviews 2007, Issue 2. Edited (no change to conclusion), published in Issue 4, 2009.
Study Type / Methods	Systematic Review and meta-analysis

The objective of this review was to assess the effects of long-term treatment with long-acting insulin analogues (insulin glargine and insulin detemir) compared with NPH insulin in patients with type 2 diabetes mellitus.

The Cochrane Library[including the Cochrane Controlled Trials Register (CENTRAL)], MEDLINE, EMBASE and CRD Databases (DARE, NHSEED, HTA) via Ovid Web Gateway were searched. Additional searching by using cross-references from original articles, inquiries to pharmaceutical companies and contacted experts and approval agencies.

Two authors independently selected trials for inclusion. Data from each included trial were extracted by two independent authors using data extraction form. The selection criteria include randomised controlled trials in adults with diabetes mellitus type 2 and had a trial duration of at least 24 weeks.

Assessment for methodological quality was done using a modification of the criteria given in the Cochrane Handbook for Systematic Reviews of Interventions and the criteria of Schulz and Jadad.

Weighted mean differences (WMD) were calculated for the percentage of glycosylated haemoglobin and random effects model was used for the meta-analysis. Sensitivity analysis was performed. |
| **LE** | I |
| **Number of patients & Patient characteristics** | A total of 8 studies were included:-

• 6 studies investigated insulin glargine

• 2 studies investigated insulin determir

• 1,715 patients were randomised to insulin glargine

• 578 patients were randomised to insulin detemir

• Mean duration of diabetes ranged from 8 to 14 years

• Mean age ranging from 55 to 62 years

• Most patients were overweight, BMI ranging from 27 to 33 kg/m^2

• Duration of included studies ranged from 24 to 52 weeks

• All include trials had a multi-centre design ranging from 7 to 111 centres. |
Intervention	Long-acting insulin analogues (insulin glargine or insulin detemir)
Comparison	NPH insulin
Length of follow up (if applicable)	

Outcome measures/ Effect size	**a. Severe hypoglycaemia**
	
	Peto-Odds Ratio (Peto-OR)
	• **(Glargine versus NPH, 4 studies 2,207 patients):-**
	  Peto-OR and 95% confidence interval (CI) = [0.70 (0.40 to 1.23)] I^2 = 26.0%
	• **(Insulin detemir versus NPH, 2 studies, 980 patients):-**
	  Peto-OR and 95% confidence interval (CI) = [0.50 (0.18 to 1.38)] I^2 = 44.0%
	
	b. Symptomatic hypoglycaemia
	(Glargine versus NPH, 3 studies 1,458 patients):-
	Peto-OR and 95% confidence interval (CI) = [0.84 (0.75 to 0.95)] I^2 = 44.0%
	
	c. Overall hypoglycaemia
	• **(Insulin detemir versus NPH, 2 studies, 980 patients):-**
	  Peto-OR and 95% confidence interval (CI) = [0.82 (0.74 to 0.90)] I^2= 0.0%
	
	d. Nocturnal hypoglycaemia
	• **(Glargine versus NPH, 3 studies 1,458 patients):-**
	  Peto-OR and 95% confidence interval (CI) = [0.66 (0.55 to 0.80)] I^2 = 33.0%
	• **(Insulin detemir versus NPH, 2 studies, 980 patients):-**
	  Peto-OR and 95% confidence interval (CI) = [0.63 (0.52 to 0.76)] I^2 = 0.0%
	
	e. Adverse events
	• **Glargine or determir versus NPH**
	  - Number of adverse events were comparable for all treatment arms
	
	f. Mortality
	• No study was designed or adequately powered to investigate mortality
	
	Authors conclusion
	
	Our analysis suggests, if at all only a minor clinical benefit of treatment with long-acting insulin analogues for patients with diabetes mellitus type 2 treated with basal insulin regarding symptomatic nocturnal hypoglycaemic events. Until long-term efficacy and safety data are available, we suggest a cautious approach to therapy with insulin glargine or detemir.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Peto odds ratio (OR) 95% CI 7. CI is not wide

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Evidence Table	**: Safety**
Question	**: Is long-acting insulin analogues safe for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	15. Waugh N, Cummins E, Royle P, Clar C, Marien M, Richter B, Philip S. Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. Health Technology Assessment 2010; Vol. 14: No. 36. Health Technology Assessment NIHR HTA programme.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to review the newer agents available for blood glucose control in type 2 diabetes from four classes: the glucagon-like peptide (GLP-1) analogue exenatide; dipeptidyl peptidase-4 (DPP-4) inhibitors sitagliptin and vildagliptin; the long-acting insulin analogues, glargine and determir; and to review concerns about the safety of thiazolidinediones. Databases searched: MEDLINE (1990-April 2008), EMBASE (1990-April 2008), the Cochrane Library (all sections) Issue 2, 2008, and the Science Citation Index and ISI Proceedings 2000-April 2008). Identify good quality systematic reviews and then looked for new trials published since the reviews. Combined the new trials with the relevant older ones in an updated meta-analyses. Data extraction was carried out by one person and checked by a second. Studies were assessed for quality using standard methods for reviews of trials. Meta-analyses were carried out using the Cochrane Review Manager (Revman) software. Modelling of cost-effectiveness of the various regimes used the United kingdom Prospective Diabetes Study (UKPDS) outcomes Model.
LE	I
Number of patients & Patient characteristics	3 Good quality systematic reviews:- • Horvath *et al.* (Cochrane review, 2007) • Tran *et al.* (CADTH, 2007) • Warren *et al.* (UK HTA, 2004) The 3 systematic reviews included 14 RCTs of insulin Glargine and 2 RCTs of insulin Detemir. Three new RCTs identified:- • Montana (2007) • Philis-Tsimikas (2006) • Rosenstock (2008)
Intervention	Long-acting insulin analogues (IGar or IDet)
Comparison	Conventional human insulin (HI) or oral antidiabetic drugs (OADs)
Length of follow up (if applicable)	

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Outcome measures/ Effect size	**Type 2 DM:-** **a. Hypoglycaemia** • **IGlar versus NPH** **Overall hypoglycaemia (7 trials, 2,297 patients):-** [RR (95% CI)=0.89 (0.83 to 0.96)] I^2= 0.0% **Severe hypoglycaemia (6 trials, 2,916 patients):-** [RR (95% CI)=0.82 (0.45 to 1.49)] I^2= 14.0% **Symptomatic hypoglycaemia (4 trials, 1,662 patients):-** [RR (95% CI)=0.80 (0.68 to 0.93)] I^2= 64.0% **Nocturnal hypoglycaemia (7 trials, 2,678 patients):-** [RR (95% CI)= 0.54 (0.43 to 0.69)] I^2= 58.0% • **IDet versus NPH:-** **Overall hypoglycaemia (4 trials, 1,584 patients):-** [RR (95% CI)=0.68 (0.54 to 0.86)] I^2= 80.0% **Severe hypoglycaemia (4 trials, 1,584 patients):-** [RR (95% CI)=0.59 (0.15 to 2.24)] I^2= 32.0% **Nocturnal hypoglycaemia (4 trials, 1,584 patients):-** [RR (95% CI)= 0.54 (0.42 to 0.68)] I^2= 48.0% **Authors conclusion:** Glargine and determir are equivalent to NPH in terms of glycaemic control as reflected in HbA1c level, but have modest advantages in terms of hypoglycaemia, especially nocturnal. Their cost-effectiveness is always relative, and depends on where they are used in the therapeutic pathways.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. WMD, 95% CI 7. CI is not wide INAHTA checklist for HTA report

Evidence Table	**: Safety**
Question	**: Is long-acting insulin analogue (insulin glargine) safe for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	16. Bazzano LA, Lee LJ, Shi L, Reynolds K, Jackson JA, Fonseca V. Safety and efficacy of glargine compared with NPH insulin for treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials. Diabetic Medicine.2008;25:924-932
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to systematically analyse evidence from RCTs examining the safety and efficacy of galrgine and NPH insulin in adults with Type 2 diabetes. Electronic databases were searched; MEDLINE (1966 to March 2007), EMBASE (1974 to March 2007), and the Cochrane Central Register of Controlled Trials. Search was restricted to include only human studies. No language restriction. A manual search of references cited and contacted experts in the field. Contents of abstracts and full-text identified were reviewed independently by two investigators. Studies were eligible for inclusion if they met all the inclusion and exclusion criteria. The intervention duration was at least 4 weeks. Data abstraction was completed by two independent investigators. All analyses were conducted in STATA version 8.2. Meta-analysis was conducted according to the QUOROM guidelines for the conduct and reporting of meta-analysis of RCTs.
LE	I
Number of patients & Patient characteristics	12 trials were included:- • 4,385 participants • 54.1% were male • Mean age was 58.3 years • Mean BMI was 28.4 kg/m • Mean duration of diabetes was 10.5 years • The average length of studies was 27.8 weeks, with a range of 4 to 52 weeks • Average study size was 366 participants with a range of 24 to 756 participants
Intervention	Long-acting insulin analogue (Insulin glargine)
Comparison	[Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Type 2 DM (Insulin glargine versus NPH):-** **Mean percentage of participants reporting hypoglycaemia:-** **a. Any hypoglycaemia (10 trials):-** **- NPH versus glargine** = (58.95% versus 53.01%, P= 0.0003) **b. Symptomatic hypoglycaemia (6 trials):-** **- NPH versus glargine** = (51.40% versus 42.88%, P <0.0001) **c. Nocturnal hypoglycaemia (8 trials):-** **- NPH versus glargine** = (33.25% versus 19.10%, P <0.0001) **d. Confirmed hypoglycaemia (2 trials):-** **- NPH versus glargine** = (9.97% versus 6.30%, P=0.11) **e. Severe hypoglycaemia (7 trials):-** **NPH versus glargine** = (2.5% versus 1.4%, P=0.07) **Authors conclusion** We identified no difference in glucose-lowering between insulin glargine and NPH insulin, but less patient reported hypoglycaemia with glargine and slightly less weight gain with NPH in adults with type 2 diabetes.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Mean %, P value 7. No CI

Evidence Table	: Safety
Question	: Is long-acting insulin analogue (insulin glargine) safe for treatment of type 2 diabetes mellitus compared to human insulin?

Bibliographic citation	17. Mu P, Lu H, Zhang G, Yanning C, Fu J, Wang M, Shu J, Zeng L. Comparison of fasting capillary glucose variability between glargine and NPH. Diabetes Research and Clinical Practice.2011:e4-e7
Study Type / Methods	Randomised controlled trial (RCT) in China The objective of this study was to investigate the glycaemic variability between insulin glargine and NPH Type 2 diabetes mellitus (DM) patients were randomly assigned into two groups for basal insulin therapy at bedtime: insulin glargine or human NPH insulin. Patients were selected based on inclusion and exclusion criteria. The doses of insulin were titrated to attain the goal which was defined as fasting blood glucose (FBG < 6.0 mmol/L). The regimens were maintained for 3 months after the target was reached.
LE	II-I

Number of patients & Patient characteristics	A total of 260 adults with type 2 diabetes mellitus were included:-
	- 130 treated with glargine
	- 130 treated with NPH insulin
	
	Baseline characteristics were similar between two groups:-
	• Insulin glargine group [Mean± SD)]:-
	  - Age = 40.3 ± 8.5
	  - Diabetes duration (years) = 4.9 ± 2.6
	  - HbA1c (%) = 9.82 % ± 1.56
	  - FPG (mmol/L) = 10.21 ± 2.82
	  - 2 h PPG (mmol/L) = 16.2 ± 4.33
	  - CV-FBG (%) =13.4 ± 3.6
	  - 44.4% male, 55.6% female
	
	• NPH insulin group (Mean ± SD):-
	  - Age = 40.6 ± 8.3
	  - Diabetes duration (years) = 4.7 ± 2.4
	  - HbA1c (%) = 9.68 % ± 1.73
	  - FPG (mmol/L) = 10.52 ± 2.63
	  - 2 h PPG (mmol/L) = 15.8 ± 3.97
	  - CV-FBG (%) = 9.68 ± 1.73
	  - 41.3% male, 58.7% female

Intervention	Insulin glargine
Comparison	NPH insulin
Length of follow up (if applicable)	3 months
Outcome measures/ Effect size	Overall, a total of 250 patients [124 (95.3%) in the insulin glargine group and 126 (96.9%) in the NPH insulin group] completed the study:- - Patients withdrawal was the reason for study discontinuation **At the end of the study:-** Hypoglycaemic episodes • Incidence was not significantly lower in the insulin glargine group [6 of 124 (4.84%)] than in the NPH group [9 of 126 (7.14%)] • No severe hypoglycaemic episodes occurred during the study period **Authors conclusion** Our results demonstrated that insulin glargine was more potent in improving glycaemic control than NPH with stable fasting blood glucose and without increasing hypoglycaemia in inadequately controlled Type 2 DM with oral anti diabetics alone.
General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Safety**

Question : **Is long-acting insulin analogue (insulin glargine) safe for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	18. Mattia GD, Laurenti O, Moretti A. Comparison of glycaemic control in patients with type 2 diabetes on basal insulin and fixed combination of oral antidiabetic treatment: results of a pilot study. Acta Diabetol.2009; 46:67-73
Study Type / Methods	Randomised controlled trial (RCT) in Italy The aim of this study was to determine either by CGMS or by venous plasma glucose excursion measurement the relative impact of isulin glargine and NPH insulin on FBG and postprandial glucose handling after a mixed meal in patients with type 2 diabetes mellitus Randomised, controlled, open-label, national, single centre, two- way cross-over study. The study comprised a 1-week run-in-phase, followed by two 12-week treatment phases and 2-week safety follow-up phase. At visit 2 (baseline) patients were randomised to either Sequence A (glargine followed by NPH insulin) or sequence B (NPH insulin followed by insulin glargine). Study drugs were cross-over after 12 weeks of treatment.
LE	II-I
Number of patients & Patient characteristics	A total of 21 patients with type 2 diabetes mellitus were included of whom 10 were assigned to Sequence A and 11 were assigned to Sequence B Baseline characteristics of patients Mean± SD):- - Age (years) = 59. ± 8.2 - 70% male, 30% female - HbA1c (%) = 9.3 % ± 1.4 - Weight (kg) = 82.7 ± 8.7 - BMI (kg/m²) = 29.5 ± 2.0 - Fasting blood glucose (mg/dL) = 203.6 ± 58.3
Intervention	Insulin glargine plus OADs
Comparison	NPH insulin plus OADs
Length of follow up (if applicable)	27 weeks

Outcome measures/ Effect size	20 patients (95.2%) completed the total study period. One patient assigned to sequence A discontinued the study at visit 2 owing to consent withdrawal.
	
	 a. Hypoglycaemia
	 • 13 insulin glargine treated patients and 15 NPH insulin treated patients experienced at least one episode of hypoglycaemia during treatment
	 • Overall Incidence of hypoglycaemia:-
	    - Insulin glargine = 1.04 episodes/patient/per month
	    - NPH insulin = 2.12 episodes/patient/per month
	
	 b. Adverse events:-
	    - Insulin glargine group - 3 patients (none considered to be related to study drug).
	
	 Authors conclusion
	
	 Adding insulin glargine to existing OADs is more effective in reducing postprandial blood glucose fluctuations during the day compared with NPH insulin plus OADs, with lower incidence of hypoglycaemia.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table	**: Safety**
Question	**: Is long-acting insulin analogues (insulin glargine) safe for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	19. Home PD, Fritscher A, Schinzel S, Massi-Benedetti M. Meta-analysis of individual patient data to assess the risk of hypoglycaemia in people with type 2 diabetes using NPH insulin or insulin glargine. Diabetes, obesity and Metabolism. 2010;12:772-779
Study Type / Methods	Systematic Review and meta-analysis

The objective of this study was to assess the risk (odds ratio and absolute risk reduction) of hypoglycaemia with once-daily evening or morning regimens of glargine, compared with once-daily NPH.

Systematic review of literature was performed using bibliographic databases and literature registries of secondary publications with a time-frame from June 2000 to end-December 2007. Studies with available individual patient data (IPD) were identified based on search and inclusion criteria set by Institute for Quality and Efficiency in Health Care (IQWiG), namely RCTs of at least 24 weeks duration per treatment, including type 2 DM who received comparable dosing regimens and algorithms of basal glargine versus basal NPH in combination with oral glucose lowering drugs (OGLDs), but no meal time insulin.

All studies included were conducted according to the Declaration of Helsinki and fulfilled the criteria of the CONSORT and QUOROM statements.

Four categories of hypoglycaemic events were examined: symptomatic hypoglycaemia with plasma glucose (PG) <2.0 mmol/L, symptomatic hypoglycaemia with plasma glucose (PG) <3.9 mmol/L, severe hypoglycaemia and total hypoglycaemia.

Two separate analyses based on two distinct 'pools' of studies identified from the literature search.

Study pool 1 included IPD from trials of once-daily evening regimens of glargine and NPH in combination with OGLDs, and study pool 2 included include data from people receiving morning glargine, compared with once-daily evening administration of NPH. |
| **LE** | I |
| **Number of patients & Patient characteristics** | 5 studies were included in pool 1 (evening glargine) and one study in pool 2 (morning glargine):-
• Treatment duration was 24 to 28 weeks in four studies and 52 weeks in one study.
• Comprised of 2,711 people (1,335 used glargine and 1,376 used NPH) and pool 2 comprised 470 people (glargine 237 and NPH 233).
• Baseline characteristics were well balanced between the two insulin groups within each pool
• Mean age of nearly 60 years
• Mean body mass index ~ 29 kg/m^2
• Mean diabetes duration was 10 years |
Intervention	Long-acting insulin analogue (Insulin Glargine)
Comparison	[Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Pool 1 (evening glargine, 5 trials, 2,641):-**

Hypoglycaemia

a. Daytime hypoglycaemia
• **Severe**
  [Odds ratio (OR) with 95% confidence interval (CI) = 1.01 (0.49 to 2.07, P= 0.988)]
• **Symptomatic, PG<2.0 mmol/L**
  [OR with 95% CI = 0.64 (0.39 to 1.04, P=0.073)]
• **Symptomatic, PG<3.9 mmol/L**
  [OR with 95% CI = 0.88 (0.75 to 1.04, P= 0.136)]

b. Nocturnal hypoglycaemia
• **Severe**
  [Odds ratio (OR) with 95% confidence interval (CI) = 0.52 (0.27 to 1.00, P= 0.049)]
• **Symptomatic, PG<2.0 mmol/L**
  [OR with 95% CI = 0.44 (0.25 to 0.76, P= 0.003)]
• **Symptomatic, PG<3.9 mmol/L**
  [OR with 95% CI = 0.52 (0.35 to 0.76, P= 0.009)] |

Outcome measures/ Effect size (Con't)	c. Total hypoglycaemia • **Severe** [Odds ratio (OR) with 95% confidence interval (CI) = 0.74 (0.25 to 2.23, P= 0.494)] • **Symptomatic, PG<2.0 mmol/L** [OR with 95% CI = 0.51 (0.35 to 0.76, P= 0.001)] • **Symptomatic, PG<3.9 mmol/L** [OR with 95% CI = 0.64 (0.46 to 0.88, P= 0.018)] **Pool 2 (morning glargine, 1 trial, 462 people):-** **Hypoglycaemia** **a. Daytime hypoglycaemia** • **Severe** [[Odds ratio (OR) with 95% confidence interval (CI) = 1.40 (0.32 to 6.05, P= 0.653)] • **Symptomatic, PG<2.0 mmol/L** [OR with 95% CI = 0.75 (0.16 to 3.48, P= 0.715)] • **Symptomatic, PG<3.9 mmol/L** [OR with 95% CI = 1.28 (0.86 to 1.89, P= 0.224)] **b. Nocturnal hypoglycaemia** • **Severe** [Odds ratio (OR) with 95% confidence interval (CI) = 0.16 (0.00 to 1.30, P= 0.090)] • **Symptomatic, PG<2.0 mmol/L** [OR with 95% CI = 0.64 (0.06 to 7.26, P= 0.715)] • **Symptomatic, PG<3.9 mmol/L** [OR with 95% CI = 0.20 (0.11 to 0.34, P< 0.001)] c. Total hypoglycaemia • **Severe** [Odds ratio (OR) with 95% confidence interval (CI) = 0.67 (0.20 to 2.28, P= 0.522)] • **Symptomatic, PG<2.0 mmol/L** [OR with 95% CI = 0.88 (0.23 to 3.40, P= 0.857)] • **Symptomatic, PG<3.9 mmol/L** [OR with 95% CI = 0.78 (0.53 to 1.15, P= 0.209)] **Number needed to treat (NNT)** **Pool 1 (evening glargine, 5 trials, 2,641):-** **a. Nocturnal hypoglycaemia (random effects model)** • **Symptomatic, PG<3.9 mmol/L** [NNT with 95% CI = 8 (6 to 13, P< 0.001)] • **Any nocturnal hypoglycaemia** [NNT with 95% CI = 8 (6 to 13, P< 0.001)] **b. Total hypoglycaemia (random effects model)** • **Symptomatic, PG<3.9 mmol/L** [NNT with 95% CI = 9 (6 to 19, P< 0.001)] • **All total hypoglycaemia** [NNT with 95% CI = 11 (8 to 18, P< 0.001)] **Pool 2 (morning glargine, 1 trial 462 people) :-** **a. Nocturnal hypoglycaemia (random effects model)** • **Symptomatic, PG<3.9 mmol/L** [NNT with 95% CI = 5 (4 to 7, P < 0.001)] • **All nocturnal hypoglycaemia** [NNT with 95% CI = 5 (4 to 7, P < 0.001)] **Authors conclusion:** This meta-analysis of open-label studies provides confidence that reductions of around 50% of risk for nocturnal hypoglycaemia can be achieved with using glargine instead of NPH. Approximately eight people or less need to be treated to save one patients from experiencing such an event in about half a year.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. OR, CI and P value, NNT 7. CI some wide and some not wide

Evidence Table **: Safety**

Question **: Is long-acting insulin analogues (insulin glargine) safe for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	20. Rosenstock J, Fonseca V, McGill JB, Riddle M, Halle JP, Hramiak I, Johnston P, Davis M. Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. Diabetologia. 2009;52:1778-1788
Study Type / Methods	Randomised controlled trial (RCT) in United States and Canada. The aim of this study was to further characterise the retinal safety profile in insulin glargine and human protamine Hagedorn (NPH) insulin in patients with type 2 diabetes mellitus. 5 year, multicentre, multinational (USA and Canada) randomised (1:1), open-label, human NPH insulin-controlled, parallel-group study in patients with type 2, diabetes and either no or non-proliferative retinopathy [less than severe; Early Treatment Diabetic Retinopathy Study (ETDRS) level less than 53 in both eyes] who were treated with oral hypoglycaemic agents (OHAs) alone, insulin alone or OHAs with insulin for $\geq$ 3 months prior to study entry and a baseline HbA1c level of 6.0 to 12.0%. Patients were randomised by the investigator according to the centralised interactive voice response system to receive twice-daily NPH insulin (n=509) or once-daily basal insulin glargine (n=515). Diabetic retinopathy status was assessed in seven-field stereoscopic fundus photographs obtained at screening and after 3, 6, 12, 24, 36, 48 and 60 months of treatment. Photographs underwent treatment-group-masked grading without comparison with other photographs. To verify progression status, a side-by-side comparison of baseline and follow-up photographs masked to treatment was conducted by a senior grader for any patient whose ETDRS score demonstrated a three step or greater progression over baseline at any time point during the study.
LE	II-I
Number of patients & Patient characteristics	A total of 1,024 adults with type 2 diabetes mellitus were included:- - 515 treated with glargine - 509 treated with NPH insulin Baseline characteristics were generally similar between two groups:- • Insulin glargine group [Mean± SD)]:- - Age (years) = 54.9 ± 8.8 - 54.2% male, 45.8% female - Diabetes duration (years) = 10.7 ± 6.9 - HbA1c (%) =8.41 % ± 1.38 - Weight (kg) = 100.2 ± 22.7 - Duration of prior treatment with insulin (years) = 5.5 ± 6.6 - Moderate NPDR or worse (level 43/<43 or worse) =53 ± 10.3 • NPH insulin group (Mean ± SD):- - Age (years)= 55.3 ± 8.5 - 53.6% male, 46.4% female - Diabetes duration (years) = 10.8 ±6.7 - HbA1c (%) = 8.31% ±1.38 - Weight (kg) = 98.7 ± 22.3 - Duration of prior treatment with insulin (years) = 4.9 ± 5.1 - Moderate NPDR or worse (level 43/<43 or worse) =53 ± 10.3
Intervention	Insulin glargine
Comparison	NPH Insulin
Length of follow up (if applicable)	5 years

Outcome measures/ Effect size	Overall, a total of 737 patients completed the study [374 (72.6%) in the insulin glargine group and 364 (72.2%) in the NPH insulin group] completed the study (per protocol analysis):-
	
	- In the glargine group, 139 premature withdrawal
	- In the NPH group, 140 premature withdrawal
	
	Intention to treat (ITT) analysis (n=513 in glargine group) and (504 in NPH insulin group)
	
	At the end of the study (ITT):-
	
	a. Changes in Diabetic retinopathy (baseline to endpoint change), per protocol analysis:-
	
	• Patients with ≥ 3 step progression in ETDRS score at endpoint (n/%) :-
	  - Insulin glargine group = 53/374 (14.2%)
	  - Insulin NPH group = 57/363 (15.7%)
	  - Difference between groups= (Mean ± SEM, 95% CI) = [-1.98% ± 2.57 (-7.02 to 3.06%)]
	
	• Development of proliferative diabetic retinopathy during the study:-
	  - Insulin glargine group = 20/373 (5.4%),
	  - Insulin NPH group = 14/363 (3.9%) P = 0.5064
	
	• Development of clinically significant macular oedema (CSMO) during the study:-
	  - Insulin glargine group = 58/371 (15.6%),
	  - Insulin NPH group = 53/362 (14.6%) P = 0.7674
	
	b. Hypoglycaemia (ITT)
	
	Patients with hypoglycaemic events (n/%):-
	
	• Symptomatic hypoglycaemia:-
	  - Insulin glargine group = 370 (73.9%),
	  - Insulin NPH group = 385 (77.9%) P = 0.1366
	
	• Symptomatic nocturnal hypoglycaemia:-
	  - Insulin glargine group = 281 (56.1%),
	  - Insulin NPH group = 296 (59.9%) P = 0.2248
	
	• Severe hypoglycaemia:-
	  - Insulin glargine group = 38 (7.6%),
	  - Insulin NPH group = 55 (11.1%) P = 0.0439
	
	Patients mean yearly rate of hypoglycaemia (Mean±SD) :-
	
	• Symptomatic hypoglycaemia:-
	  - Insulin glargine group = 5.13 ± 12.79
	  - Insulin NPH group = 7.08 ± 16.49 P = 0.0017
	
	• No significant difference for symptomatic nocturnal hypoglycaemia and severe hypoglycaemia.
	
	c. Adverse events
	
	Rates of adverse events were similar for the two treatments.
	
	Authors conclusion
	
	This study shows no evidence of a greater risk of the development or progression of diabetic retinopathy with insulin glargine versus NPH insulin treatment in patients with type 2 diabetes.

General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

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Evidence Table	**: Safety**
Question	**: long-acting insulin analogues (insulin glargine) safe in treatment of diabetes in pregnancy compared with human insulin?**

Bibliographic citation	21. Pollex E, Moretti ME, Koren G, Feig DS. Safety of insulin glargine use in pregnancy: A systematic Review and Meta-Analysis. The Annals of Pharmacotherapy.2011;45:XXXX.
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to determine the foetal safety of insulin glargine use in the treatment of diabetes in pregnancy compared with NPH insulin therapy. A systematic literature search was conducted using MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Controlled Trials database, and Web of Science from 1980 to June 1, 2010. Additional studies were identified by hand-searching reference lists from review articles. The inclusion criteria for the selection of papers consisted of studies that were either case-control, cohort, or randomised controlled trials. Two reviewers independently reviewed all citations identified by the systematic search. The two reviewers individually performed an assessment of the quality of the observational studies suing the Strengthening of the Reporting of Observational Studies in epidemiology Criteria Assessment tool. Standardised forms were used to subsequently extract information from each article that met the inclusion criteria. Data were combined using random effects model. Relative risk and weighted mean difference were calculated. I^2 values of 25%, 50%, and 75% were considered to indicate low, medium, and high heterogeneity, respectively.
LE	I

Number of patients & Patient characteristics	A total of 8 studies were included:-
	
	• All of the included studies were observational cohort studies.
	
	• Each study included pregnant women with either gestational diabetes or pregestational diabetes who were on insulin glargine and a control group of women on NPH insulin in pregnancy.
	
	• A total of 702 women:-
	  - 331 treated with insulin glargine
	  - 371 treated with NPH insulin

Intervention	long-acting insulin analogue (insulin glargine)
Comparison	NPH Insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Foetal / Neonatal Outcomes:-** **a. Large for gestational age (birth weight >90th percentile)** • **(Insulin glargine versus NPH insulin, 5 studies):-** Relative risk (RR) and 95% confidence interval (CI) = [1.02 (0.80 to 1.31)] **b. Macrosomia (birth weight >4000g)** • **(Insulin glargine versus NPH insulin, 3 studies, 391 infants:-** Relative risk (RR) and 95% confidence interval (CI) = [1.28 (0.77 to 2.12)] I^2 = 0% **c. Neonatal hypoglycaemia** • **(Insulin glargine versus NPH insulin, 7 studies, 650 neonates):-** Relative risk (RR) and 95% confidence interval (CI) = [0.94 (0.64 to 1.39)] I^2 = 22%

Outcome measures/ Effect size (Con't)	**d. Congenital anomalies** • **(Insulin glargine versus NPH insulin, 5 studies, 335 neonates):-** Relative risk (RR) and 95% confidence interval (CI) = [0.97 (0.47 to 1.99)] $I^2 = 0\%$ **e. NICU admissions** • **(Insulin glargine versus NPH insulin, 6 studies):-** Relative risk (RR) and 95% confidence interval (CI) = [0.89 (0.55 to 1.43)] **f. Shoulder dystocia** • **(Insulin glargine versus NPH insulin, 2 studies):-** Relative risk (RR) and 95% confidence interval (CI) = [0.22 (0.04 to 1.29)] **g. Preterm deliveries** • **(Insulin glargine versus NPH insulin, 2 studies):-** Relative risk (RR) and 95% confidence interval (CI) = [0.75 (0.30 to 1.83)] **h. Perinatal mortality** • **(Insulin glargine versus NPH insulin, 4 studies):-** Relative risk (RR) and 95% confidence interval (CI) = [0.97 (0.18 to 5.37)] **i. Hyperbilirubinemia** • **(Insulin glargine versus NPH insulin, 6 studies):-** Relative risk (RR) and 95% confidence interval (CI) = [0.95 (0.59 to 1.54)] **j. Respiratory distress** • **(Insulin glargine versus NPH insulin, 6 studies):-** Relative risk (RR) and 95% confidence interval (CI) = [1.53 (0.82 to 2.85)] **Authors conclusion** No evidence has been documented for increased adverse foetal outcomes with the use of insulin glargine in pregnancy compared with the use of NPH insulin. The results increase the choices for women requiring basal insulin in pregnancy.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. RR, 95% CI 7. CI is not wide

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Evidence Table	**: Safety**
Question	**: Is long-acting insulin analogues (insulin detemir) safe for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	22. Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S, Jones RH, Umpleby A, Russel-Jones D. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care. 2011;34:1487-1491
Study Type / Methods	Randomised controlled trial (RCT) in United Kingdom The objective of this study was to investigate whether this effect was a result of reduced energy intake and/or increased energy expenditure A randomised, single centre, open-labelled, crossover design trial was undertaken in 23 patients with type 1 diabetes. Patients on a basal-bolus regimen (with insulin aspart as the bolus insulin) were randomly assigned to insulin detemir or NPH insulin as a basal insulin for 16 weeks, followed by the other basal insulin for 16 weeks. At the end of the of each 16 weeks period, total energy expenditure, energy intake, weight change, glycaemic control, hypoglycaemic episodes, and hormones that affect safety and fuel partitioning were measured. During the trial, subjects attended the hospital for eight planned visits, and the investigator was in contact with the patients by telephone at least 10 times.
LE	II-I
Number of patients & Patient characteristics	A total of 23 patients with type 1 diabetes mellitus were included in the study. - Male to female ratio; 14 to 9 - Average age (mean ± SE) = 38.8 ± 2.17 years - Average weight (mean ± SE) = 81.9 ± 2.21 kg - BMI (mean ± SE) = 28 ± 3.6 kg/m^2 - Duration of diabetes (mean ± SE) = 19.95 ± 2.09 years - HbA1c (mean ± SE) = 8.2 ± 0.22%
Intervention	Insulin detemir
Comparison	NPH insulin
Length of follow up (if applicable)	32 weeks
Outcome measures/ Effect size	Overall, a total of 22 patients (95.6%) completed the study:- - One patient did not complete the trial for personal reasons **After 16 weeks of treatment** **Hypoglycaemic episodes (< 3.1 mmol/L)** • No significant difference between insulin detemir (4.6 ± 1.58) versus NPH insulin (4.9 ± 1.53), P= 0.586 • No major hypoglycaemic episodes (defined as patients unable to treat themselves) in the trial **Authors conclusion:** The reduced weight gain with the insulin detemir compared with NPH insulin is attributed to reduced energy intake rather than increased energy expenditure. This may be mediated by a direct or indirect effect of insulin detemir on the hormones that control satiety.
General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

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Evidence Table : **Safety**

Question : **Is long-acting insulin analogues (insulin determir) safe for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	23. Szypowska A, Golicki D, Groele L, Pankowska E. Long-acting insulin analogue determir compared with NPH insulin in type 1 diabetes. A systematic review and meta-analysis. Polskie Archiwum Medycyny Wewnetrznej. 2011;121(7-8): 237-245
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to compare the effect of treatment with detemir insulin versus NPH insulin in metabolic control, hypoglycaemic episodes, and body weight gain in patients with type 1 diabetes. Electronic databases were systematically searched; MEDLINE (PubMed), EMBASE (Ovid), the Cochrane Database of Systematic Reviews for randomised clinical trials on humans up to November 2010.Reference lists from original studies and review articles were screened. The Novo Nordisk trial register was searched for unpublished trials. No restrictions in language. Data extraction was performed independently by two reviewers. The duration of studies at least 12 weeks. The quality of studies that met the inclusion criteria was assessed independently by reviewers without blinding to authorship or journal. Comprehensive Meta-analysis ver. 2 software was used.
LE	I

Number of patients & Patient characteristics	10 studies met the inclusion criteria:-
	
	• 7 full-text articles
	
	• 3 unpublished trials
	
	• 3,825 patients with type 1
	
	   - 3,048 adults
	
	   - 777 children
	
	• All trials contained sufficient proportion (≥ 80%) of participants in the final analysis.
	
	• Duration of intervention ranged from 4 to 24 months.
	
	• 9 parallel-group design, one was crossover study.
	
	• All studies were open-label, as detemir and NPH are visually distinguishable and patients self-administered insulin.

Intervention	Long-acting insulin analogue (Insulin Detemir)
Comparison	[Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Type 1 DM (Detemir versus NPH):-**
	a. All-day hypoglycaemic episodes:-
	• **(8 trials, 3,096 patients)**
	[RR (95% CI)= 0.978 (0.961 to 0.996, P= 0.016)] I^2= 26.0%
	Estimated risk difference (RD) = -0.02 (95%CI; -0.037 to -0.003, P= 0.02)
	b. All nocturnal hypoglycaemic episodes:-
	• **(8 trials, 3,304 patients)**
	[RR (95% CI)= 0.877 (0.816 to 0.942, P<0.001)] I^2= 51.0%
	Estimated risk difference (RD) = -0.0076 (95%CI; -0.116 to -0.036, P < 0.001)
	c. Severe or major hypoglycaemic episodes:-
	• **(8 trials, 3,149 patients)**
	[RR (95% CI)= 0.665 (0.547 to 0.810, P<0.001)], I^2=0.0%
	Estimated RD= -0.028 (95%CI; -0.049 to -0.007, P= 0.008)
	d. Severe or major nocturnal hypoglycaemic episodes:-
	• **(6 trials, 2,642 patients)**
	[RR (95% CI)= 0.687 (0.392 to 1.204, P <0.189)] I^2= 52.0%
	Authors conclusion:
	Basal-bolus treatment with insulin detemir, as compared with NPH insulin, provided a minor benefit in terms of the HbA1c value and significantly reduced FPG in type 1 diabetic patients. Treatment with detemir insulin was superior to NPH insulin in reducing the risk of all-day, nocturnal, and severe hypoglycaemic episodes, with the added benefit of reduced weight gain.
General comments	Quality assessment (CASP)
	1. Yes
	2. Yes
	3. Yes
	4. Yes
	5. Yes
	6.RR, CI and P value
	7.CI not wide

Evidence Table	**: Safety**
Question	**: Is long-acting insulin analogues (insulin detemir) safe for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	24. Thalange N, Bereket A, Larsen J, Hiort LC, Peterkova V. Treatment with insulin detemir or NPH insulin in children aged 2-5 yr with type 1 diabetes mellitus. Pediatric Diabetes.2011;12: 632-641
Study Type / Methods	Randomised controlled trial (RCT) in India The objective of this study was to compare the efficacy and safety of treatment with insulin detemir (IDet) and neutral protamine Hagedorn (NPH) insulin in this vulnerable age group (2 to 5 years) after 52 weeks of treatment. 52-weeks, multinational, open-labelled, randomised (IDet: NPH) two-armed parallel group trial involving 82 children aged between 2 and 5 years, recruited from diabetes clinics at 32 sites in 10 countries. Both treatment groups received insulin aspart as bolus insulin with main meals and large snacks. The trail consisted of a 2-weeks screening period, followed by a 52-weeks titration and treatment period, including a total of 10 scheduled visits to the clinical trial sites and 8 telephone contacts. Eligible subjects were allocated to treatment with IDet or NPH in a 1:1 ratio and randomisation was carried out using a centralised telephone and web-based randomisation system, the Interactive Voice Response System (IVRS), and performed within 2 weeks after screening visit. Since IDet and NPH were easily distinguishable by visual inspection, and as the primary end-point, HbA1c was not easily biased, an open-labelled study design was chosen.
LE	II-I
Number of patients & Patient characteristics	A total of 82 children with type 1 diabetes mellitus were included:- - 42 treated with IDet - 40 treated with NPH • IDet group [Mean (SD)]:- - Age = 4.3 (1.2) - Diabetes duration (yr) = 2.2 (1.0) - HbA1c (%) = 8.2 (4.9%) - FPG (mmol/L) = 8.4 (4.9) - 57.1% female, 42.9% male • NPH group (Mean ± SD):- - Age = 4.5 (1.0) - Diabetes duration (yr) = 2.1 (0.8) - HbA1c (%) = 8.1 (1.2) - FPG (mmol/L) = 8.6 (4.1) - 47.5% female, 52.5% male
Intervention	Iinsulin detemir (IDet)
Comparison	Neutral protamine Hagedorn (NPH)
Length of follow up (if applicable)	52 weeks

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Outcome measures/ Effect size	41 (97.6%) subjects in the IDet and 39 (97.5%%) in the NPH group completed the study:-
	
	- One child withdrew from the IDet group due to adverse events and one child withdrew from the NPH group due to ineffective therapy.
	
	a. Hypoglycaemic episodes
	
	• Severe hypoglycaemic episodes
	
	  - IDet group (no severe hypoglycaemic episodes were reported)
	
	  - NPH group (6 episodes in three subjects)
	
	• Mean rate (episodes per patient-year of exposure (IDet versus NPH):-
	
	  - Total hypoglycaemic events (50.6 versus 78.3)
	
	  - Nocturnal (8.0 versus 17.4)
	
	b. Adverse events:-
	
	• Lower proportion of subjects reported adverse events with IDet than with NPH (69.0% versus 77.5%)
	
	• Serious adverse events – (5 with IDet and 7 with NPH)
	
	• Rate of severe adverse events:-
	
	  - IDet (122/1000 exposure years)
	
	  - NPH (179/100 exposure years
	
	  - The most common serious adverse events were infections (gastroenteritis) and gastrointestinal disorders (dyspepsia) in both treatment groups.
	
	  - No deaths were reported in this trial
	
	Authors conclusion:
	
	Basal-bolus treatment with insulin detemir, as compared with NPH insulin, provided a minor benefit in terms of the HbA1c value and significantly reduced FPG in type 1 diabetic patients. Treatment with detemir insulin was superior to NPH insulin in reducing the risk of all-day, nocturnal, and severe hypoglycaemic episodes, with the added benefit of reduced weight gain.

General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

Evidence Table	**: Safety**
Question	**: Is long-acting insulin analogues (insulin detemir) effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	25. Fajardo Montanana C, Hernandez Herrero C, Rivas Fernandez M. Less weight gain and hypoglycaemia with once-daily insulin detemir than NPH insulin in intensification of insulin therapy in overweight Type 2 diabetes patients-The PREDICTIVE™ BMI clinical trial. Diabet. Med.2008;25:916-923
Study Type / Methods	Randomised controlled trial (RCT) in Spain The objective of this study was to assess weight change when once-daily insulin detemir or neutral protamine Hagedorn insulin (NPH) are used in already overweight type 2 diabetes patients requiring intensifies insulin therapy A 26-week, parallel-group, randomised, controlled treat-to-target trial comparing once-daily detemir and NPH insulin in intensive insulin regimens in obese or overweight subjects with type 2 diabetes in 41 centres in Spain between September 2005 and December 2006. The trial was open-label because detemir and NPH insulin can be easily distinguished visually. At screening, subjects were randomised to receive one daily bedtime injection of either detemir or NPH insulin at approximately the same of the day, plus insulin aspart three times daily at main meals. Randomisation was stratified by centre, with each participating centre receiving sufficient sealed codes, in blocks of six. Local investigators enrolled patients and assigned them to groups by choosing the lowest available randomisation number at their site; treatment was then revealed by scratching off the protective surface of the sealed code. After randomisation, subjects made five further visits to the clinic, with the last visit at 26 weeks, and had telephone contacts between visits, 2,4 and 5. Each centre was required to use the same weighing scale throughout the trial. Statistical analyses of efficacy and safety were based on intention to treat population (all randomised subjects exposed to at least one dose of trial product)
LE	II-I

Number of patients & Patient characteristics	A total of 277 patients were randomised to treatment.
	- 126 treated with insulin detemir
	- 151 treated with NPH
	
	Baseline characteristics of patients were well matched except the NPH group contained more patients.
	
	• Insulin detemir group [Mean± SD)]:-
	  - Age = 62.1 ± 9.3
	  - Diabetes duration (years) = 16.2 ± 8.7
	  - HbA1c (%) = 8.9 % ± 0.9
	  - FPG (mmol/L) = 10.8 ± 3.5
	  - 37.6% male, 62.4% female
	  - Weight (kg) = 79.5 ± 11.9
	  - Body mass Index (kg/m^2) = 31.6 ± 4.3
	
	• NPH insulin group (Mean ± SD):-
	  - Age = 61.8 ± 8.3
	  - Diabetes duration (years) = 16.4 ± 7.4
	  - HbA1c (%) = 8.8 % ± 1.0
	  - FPG (mmol/L) = 10.1 ± 3.6
	  - 43.2% male, 56.8% female
	  - Weight (kg) = 82.2 ± 12.2
	  - Body mass Index (kg/m^2) = 32.0 ± 4.2

Intervention	Insulin detemir
Comparison	NPH insulin
Length of follow up (if applicable)	26 weeks

Outcome measures/ Effect size	Overall, a total of 258 patients (93.1%) completed the study:- - 119 (94.4%) in the detemir group and 139 (92.0%) in the NPH group - In the detemir group, one withdrew due to adverse event, three due to non-compliance and three because of other reasons - In the NPH group, two withdrew due to adverse event, two due to ineffective therapy, two due to non-compliance and five because of other reasons **Intention to treat analysis:-** - (n) =125 in the detemir group - (n) =146 in the NPH group **After 26 weeks of treatment** **a. Hypoglycaemia** • All hypoglycaemic events:- (Insulin detemir group) - 256 hypoglycaemia events were reported by 34.7% of patients (NPH insulin group) - 481 hypoglycaemia events were reported by 65.3% of patients - RR for determir versus NPH insulin =0.62, (P <0.0001) • Nocturnal hypoglycaemic events:- (Insulin detemir group) - 46 events were reported by 30.1% of patients (NPH insulin group) - 107 events were reported by 69.9% of patients - RR for determir versus NPH insulin =0.43, (P< 0.0001) • Major hypoglycaemic episodes:- (Insulin detemir group) - No episodes (NPH insulin group) - Three episodes **b. Adverse events** (Insulin detemir group) - 45 adverse events (30.8%) - 4 (2.7%) serious adverse - 3 (2.4%) adverse events resulting with withdrawal. However, only pruritus was considered related to detemir (NPH insulin group) - 58 adverse events (46.4%) - 4 (3.2%) serious adverse - No adverse events resulting with withdrawal **Authors conclusion** Use of once-daily detemir for intensification of insulin therapy resulted in less weight gain, less hypoglycaemia and equivalent glycaemic control compared with NPH.
General comments	Jadad scale Randomisation = 2 Blinding = 0 An account of all patients = 1 Total score = 3/5

Evidence Table : **Safety**

Question : **Is long-acting insulin analogues safe for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	26. Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues Versus NPH human insulin in type 1diabetes: A meta-analysis. Diabetes, Obesity and Metabolism. 2009;11:237-245.
Study Type / Methods	Systematic Review and meta-analysis The objective of this meta-analysis was to assess the differences with respect to HbA1c, incidence of hypoglycaemia, and weight gain between NPH human insulin and each long-acting analogue in type 1 diabetes. An extensive Medline search for detemir and glargine was performed, collecting all clinical trials on humans up to 1 April 20008. Unpublished trials were also searched. Identification, selection and data extraction was performed independently by two reviewers. The duration of studies at least 12 weeks. The quality of studies was assessed using Jadad scale. Comprehensive Meta-analysis ver. 2 software was used.
LE	I
Number of patients & Patient characteristics	20 trials included in the meta-analysis • 3,693 patients in insulin analogues group and 2,485 patients in the NPH group • Duration of intervention ranged from 12 to 52 weeks. • 18 parallel-series design • 18 were sponsored trials
Intervention	Long-acting insulin analogue (Insulin Detemir and Insulin Glargine)
Comparison	[Neutral Protamine Hagedorn (NPH)]
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Type 1 DM :-** **a. Any hypoglycaemia (12 trials)** • **Overall (Insulin detemir and Insulin glargine versus NPH)** Not associated with significant reduction of hypoglycaemia risk in comparison with NPH insulin. **b. Severe hypoglycaemia (16 trials)** • **Overall (Insulin detemir and Insulin glargine versus NPH)** [Mantel-Haenszel odds ratio (MH-OR) with 95% CI= 0.73 (0.60 to 0.89, P= 0.002)] **c. Nocturnal hypoglycaemia (13 trials)** • **Overall (Insulin detemir and Insulin glargine versus NPH)** [Mantel-Haenszel odds ratio (MH-OR) with 95% CI= 0.69 (0.55 to 0.86, P= 0.001)] Detemir was associated with a significantly reduced risk of severe and nocturnal hypoglycaemia incomparison with NPH.In trials with glargine, the point estimated (MH-OR) was similar to detemir, although not statistically significant. **Authors conclusion:** The switch from NPH to long-acting analogues as basal insulin replacement in type 1 diabetic patients had a small effect on HbA1c, and also reduced the risk of nocturnal and severe hypoglycaemia.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6.MH-OR, CI and P value 7.CI not wide

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Evidence Table	**: Safety**
Question	**: Is premixed Insulin analogues safe for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	27.Qayyum R,, Wilson LM, Bolen S, Maruthur N, Marinopoulus SS, Feldman L, Ranasinghe P, Amer M, Bass EB. Comparative effectiveness, safety, and indications of insulin analogues in premixed formulations for adults with type 2 diabetes. Comaparative Effectiveness Review No. 14. (Prepared by the John Hopkins University Evidence-based Practice Center). AHRQ Publication No. 08-EHCO17-EF, 2008
Study Type / Methods	Systematic Review and meta-analysis The objective of this review was to assess the effectiveness and safety of all premixed insulin analogues that are approved by the U.S. Food and Drug Administration (FDA) and available in the United States. The following databases were searched: MEDLINE (1966 to February 2008), EMBASE (1974 to February 2008), the Cochrane Central Register of Controlled Trials (CENTRAL;1966 to February 2008), CINAHL (1982 through February 2008). Hand-searched 13 journals. Also reviewed the reference lists of included studies. Two independent reviewers selected trials for inclusion. Each article underwent double review by study investigators, at the level of data abstraction and assessment of study quality. The second reviewer confirmed the first reviewer's data abstraction form for completeness and accuracy. A quality assessment tool was developed for randomised controlled trails and non randomised studies based on Jadad criteria and the Newcastle-Ottawa Scale. Meta-analyses for outcomes were conducted when there were sufficient data (two or more trials) and studies were homogenous.
LE	I
Number of patients & Patient characteristics	A total of 45 studies, represented in 50 articles were included:- • 16 studies compared premixed insulin analogues with premixed human insulin • 2 studies compared premixed insulin analogues with intermediate acting human insulin
Intervention	Premix insulin analogues (insulin aspart 70/30, insulin lispro 75/25, insulin lispro 50/50)
Comparison	Premixed human insulin (NPH/regular 70/30, NPH/regular 50/50) or NPH insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**a. Hypoglycaemia** • Premixed insulin analogues (insulin aspart 70/30, insulin lispro 75/25, and insulin lispro 50/50) were similar to premixed human insulin preparations in terms of the incidence of hypoglycaemia.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Rate ratio, 95% CI, P value

Evidence Table : **Safety**

Question : **Is premixed insulin analogues safe for treatment of type 1 or type 2 diabetes mellitus compared to premixed human insulin?**

Bibliographic citation	G, Guo X, Yuan G, Gong Q, Yan L, Zhen Y, Zhang J. Postprandial blood glucose response to a standard test meal in insulin requiring -patients with diabetes treated with insulin lisro mix 50 or human insulin mix 50. Int J Clin Pract. 2008;62(9):1344-1351
Study Type / Methods	Randomised controlled trial (RCT) in China. The aim of this study was to compare the 2-hour postprandial blood glucose (PPBG) excursion following a standard meal in insulin-requiring patients with diabetes treated twice daily with human insulin mix 50 versus lispro mix 50 (LM50). A multicentre (three centres in China), randomised, open-label, 2 sequence, 2 period, cross-over trial in patients with type 1 or type 2 diabetes treated twice daily with human insulin mix 50 versus LM50. Standard test meals were administered to compare these insulin treatments for their effect on 2-hour PPBG excursion. Patients were randomised to two groups in a 1:1 ratio, with 60 patients in each sequence group. One sequence group received twice-daily treatment with LM50, followed by 12 weeks of twice daily treatment with human insulin mix 50 (Sequence 1). The other group received the reverse treatment of the sequence 1. Diabetic retinopathy status was assessed in seven-field stereoscopic fundus photographs obtained at screening and after 3, 6, 12, 24, 36, 48 and 60 months of treatment. Photographs underwent treatment-group-masked grading without comparison with other photographs. To verify progression status, a side-by-side comparison of baseline and follow-up photographs masked to treatment was conducted by a senior grader for any patient whose ETDRS score demonstrated a three step or greater progression over baseline at any time point during the study.
LE	II-I

Number of patients & Patient characteristics	A total of 120 adults with type 1 and type 2 diabetes mellitus were included:-
	
	 Baseline characteristics were generally similar between two groups (according to sequence):-
	
	 • Sequence group 1 [Mean ± SD)]:-
	
	   - Age (years) = 54.3 ± 10.1
	
	   - 37.0% male, 63.0% female
	
	   - Diabetes duration (years) = 10.7 ± 6.9
	
	   - HbA1c (%) =8.41 % ± 1.38
	
	   - Weight (kg) = 100.2 ± 22.7
	
	   - Duration of prior treatment with insulin (years) = 5.5 ± 6.6
	
	   - Moderate NPDR or worse (level 43/<43 or worse) = 53 ± 10.3
	
	 • Sequence group 2 (Mean ± SD):-
	
	   - Age (years)= 57.2 ± 8.6
	
	   - 53.6% male, 46.4% female
	
	   - Diabetes duration (years) = 10.8 ±6.7
	
	   - HbA1c (%) = 8.31% ±1.38
	
	   - Weight (kg) = 98.7 ± 22.3
	
	   - Duration of prior treatment with insulin (years) = 4.9 ± 5.1
	
	   - Moderate NPDR or worse (level 43/<43 or worse) = 53 ± 10.3

Intervention	Lispro mix 50 (LM50)
Comparison	Human insulin mix 50
Length of follow up (if applicable)	24 weeks

Outcome measures/ Effect size	Overall, a total of 115 patients completed the study [57 (93.4%) in sequence 1 and 58 (96.7%) in sequence 2 completed the study
	
	a. Hypoglycaemia:-
	
	• Incidence of hypoglycaemia:-
	
	  - No statistically significance difference between treatment groups (P= 0.828)
	
	• Rate of hypoglycaemia per 30 days:-
	
	  - No statistically significance difference between treatment groups (P= 0.401)
	
	b. Adverse events:-
	
	- Generally well tolerated by patients
	
	- Three patients experienced serious adverse events requiring admission, one during LM50 treatment (due to pneumonia) and two during human insulin mix 50 treatment (due to coronary artery disease and hepatitis E). However, were regarded by investigators to have no relationship with either the study drug or device
	
	- Similar numbers of patients experienced at least one treatment-emergent adverse events (TEAEs) in each treatment group (39 in LM50 and 37 in human insulin mix 50). Most common TEAEs reported by patients were nasopharyngitis followed by hyperuricaemia and hypertension.
	
	Authors conclusion
	
	Insulin lispro mix 50 provided better postprandial glycaemic control compared with human insulin mix 50 while providing the convenience of injecting immediately before meals. Both treatments were generally well tolerated by all randomly assigned patients.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Safety**

Question : **Is premixed insulin analogues safe for treatment of type 1 or type 2 diabetes mellitus compared to premixed human insulin?**

Bibliographic citation	29. Li Y, Li Q, Li C, Wang C, Zheng Y, Maher I, Zhang J. Chin Med J. Comparison of HbA1c in Chinese patients with type 1 or type 2 diabetes randomized to twice daily insulin lispro low mix 25 or twice daily human insulin mix 30/70. 2009;122(21): 2540-2546
Study Type / Methods	Randomised controlled trial (RCT) in China. The aim of this study was demonstrate that twice daily insulin lispro low mix 25 is non inferior to twice daily human insulin mix 30/70 in achieveing glycaemic control as measured by HbA1c, from baseline to endpoint, in patients with type 1 or 2 3 diabetes. In this phase 1V, crossover, open-label, multicenter study, 117 Chinese patients with diabetes were randomly assigned to one of the two treatment sequence groups. One group received 12-week treatment with twice daily human insulin mix 30/70 followed by 12-week treatment with twice daily insulin lispro low mix 25, while the other group received the reverse treatment sequence. HbA1c, baseline-to-endpoint change in HbA1c, proportion of patients achieved target HbA1c $\leq$ 7% and $\leq$ 6.5%, fasting blood glucose, and daily insulin doses were measured for each period. Safety and tolerability were also assessed.
LE	II-I

Number of patients & Patient characteristics	A total of 117 patients with type 1 and type 2 diabetes mellitus were included:-
	
	- 57 patients in sequence group 1
	
	- 60 patients in sequence group 2
	
	Baseline characteristics according to sequence:-
	
	• Sequence group 1 [Mean (SD)]:-
	
	  - Age (years) = 54 (10.8)
	
	  - 45.6% male, 54.4% female
	
	  - Diabetes duration (months) = 130 (95.6)
	
	  - HbA1c (%) = 8.6 (1.3)
	
	  - Weight (kg) = 67 (12.2)
	
	  - Duration of prior treatment with insulin (months) = 39 (37.4)
	
	• Sequence group 2 (Mean $\pm$ SD):-
	
	  - Age (years)= 55 $\pm$ 10.8
	
	  - 41.7% male, 58.3% female
	
	  - Diabetes duration (months) = 130 (78.3)
	
	  - HbA1c (%) = 8.6% (1.6)
	
	  - Weight (kg) = 64 (9.6)
	
	  - Duration of prior treatment with insulin (months) = 39 (32.4)

Intervention	Insulin ispro low mix 25 (25% insulin lispro, 75% insulin protamine suspension) (LM50)
Comparison	Human insulin mix 30/70 (30% human insulin/70% NPH)
Length of follow up (if applicable)	24 weeks
Outcome measures/ Effect size	Overall, a total of 113 patients completed the study [54 (94.7%) in sequence 1 and 59 (98.3%) in sequence 2 completed the study

At the end of the study (12 weeks):-

a. Hypoglycaemia

- No statistically significant (P=0.670) difference in hypoglycaemia rate was observed between the two treatments, with an adjusted mean hypoglycaemia rate of 0.34 episodes per patient per 30 days (95% CI; 0.19 to 0.49) during human insulin mix 30/70 treatment and 0.37 episodes per patient per 30 days (95% CI; 0.22 to 0.52) during insulin lispro low mix treatment.

b. Adverse events

- Three serious adverse events were reported [human insulin mix-two patients (hypoglycaemic coma and cardiac failure) and insulin lispro mix-one patient (stroke)]. All serious adverse events were resolved.

Authors conclusion

The results support non inferiority of twice daily insulin lispro low mix 25 versus twice daily human insulin mix 30/70 in HbA1c control in Chinese patients with type 1 or type 2 diabetes. |
| **General comments** | Jadad scale

Randomisation = 1

Blinding = 0

An account of all patients = 1

Total score = 2/5 |

Evidence Table	: **Safety**
Question	: **Is premixed insulin analogues (insulin BIAspart) safe for treatment of diabetes mellitus in pregnant women compared to premixed human insulin?**

Bibliographic citation	30. Balaji V, Balaji MS, Alexander C, Ashalata S, Suganti RS, Suresh S, Seshiah V. Premixed Insulin Aspart 30 (BIAsp 300 vs Premixed Human Insulin 30 (BHI 30) in Gestational Diabetes Mellitus-A Pilot Project. JAPI.2010;58: 95-97
Study Type / Methods	Randomised controlled trial (RCT) in India The objective of this study was to compare premixed insulin aspart 30 (BIAsp 30) versus premixed human insulin 30 (BHI 30) on efficacy, safety, foetal and perinatal outcomes in pregnancies associated with gestational diabetes mellitus (GDM). 152 GDM women were randomly assigned to receive either BIASp 30 or BHI 30. GDM women in Group A were initiated on 6 units of BIASp 30 before breakfast and similarly Group B women on the same dose of 6 units BHI 30. They were instructed on self monitoring of blood glucose (SMBG) using Accucheck active and to attend antenatal clinic for routine check up monthly. Also asked to record hypoglycaemic episodes and adverse events.
LE	II-I

Number of patients & Patient characteristics	A total of 152 GDM were included:-
	- 76 treated with BIASp 30
	- 76 treated with BHI 30
	
	Baseline characteristics:- no significant difference between the two groups; P>0.05
	
	• BIAsp 30 group (Mean ± SD):-
	  - Age = 28.92 ± 3.59
	  - Body mass index; = 27.18 ± 3.87 kg/m^2
	  - Gestational weeks at entry = 22.75 ± 8.83
	  - Fasting plasma glucose (mg/dl) = 102.97 ± 18.67
	  - HbA1c (%) = 6.10 ± 0.45
	
	• BHI 30 group (Mean ± SD):-
	  - Age = 29.38 ± 4.64
	  - Body mass index; = 26.34 ± 4.02 kg/m^2
	  - Gestational weeks at entry = 22.64 ± 9.23
	  - Fasting plasma glucose (mg/dl) = 103.58 ± 20.25
	  - HbA1c (%) = 6.12 ± 0.72

Intervention	Premixed insulin analogues (BIAsp 30)
Comparison	Premixed human insulin BHI 30
Length of follow up (if applicable)	From 22nd week of pregnancy untill confinement

Outcome measures/ Effect size	There was 100% compliance and follow-up data was available for all 152 subjects.
	
	a. Hypoglycaemic episodes:-
	• No maternal hypoglycaemic episodes were observed
	
	b. Perinatal outcome:-
	• No adverse perinatal outcomes recorded
	
	c. Foetal outcome
	• Birth weight ≥ 90th percentile:-
	  - BIAsp 30 (6.8%)
	  - BHI 30 (9.2%), P>0.05
	
	Authors conclusion
	IAsp was safe during pregnancy and pregnant women found it convenient due to meal time dosing. Foetal outcome using BIAsp 30 was also comparable with BHI 30.

General comments	Jadad scale Randomisation = 1 Blinding = 0 An account of all patients = 1 Total score = 2/5

Evidence Table : **Economic**

Question : **Is long-acting insulin analogues (insulin detemir) cost-effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	1. Valentine JW, Aagren M, Haglund M, Ericsson A, Gschwend MH. Evaluation of the long-term cost-effectiveness of insulin detemir compared with neutral protamine hagedorn insulin in patients with type 1 diabetes using a basal-bolus regimen in Sweden. Scandinavian Journal of Public Health. 2011;39:79-87
Study Type / Methods	Economic evaluation. The aim of this study was to evaluate the long-term clinical and economic outcomes associated with insulin detemir and neutral protamine Hagedorn (NPH) insulin in combination with mealtime insulin aspart in patients with type 1 diabetes in Sweden, based on data from a two-year, multinational, open-label, randomised, controlled trial. Insulin detemir was associated with significant improvements in glycaemic control after 24 months (HbA1c, 7.36% versus 7.58%, mean difference -0.22%, P=0.022) and major hypoglycaemic events (69% risk reduction, P=0.001) versus NPH. Patients treated with detemir gained less weight (1.7 kg versus 2.7 kg, P=0.024). Based on these findings, a published and validated computer model (IMS CORE Diabetes Model) was used to estimate life-expectancy, quality-adjusted life expectancy and both direct medical costs and indirect costs. Costs were accounted both from a healthcare payer perspective and societal perspective, and were expressed in 2006 Swedish Kronor (SEK).Future cost and clinical outcomes were discounted at 3% per annum each. A time horizon of 50 years was used in the base case to capture costs and effects over patient lifetimes. Sensitivity analysis were performed to examine the influence of Key input parameters on outcomes projected by the model. Sensitivity analyses were performed on time horizon, discount rate, magnitude of change in HbA1c, BMI, hypoglycaemic event rates and cohort characteristics. A simulated cohort of 1000 patients was run through the model 1,000 times for each simulation (base case and sensitivity analysis).
LE	
Number of patients & Patient characteristics	Base case, Bartly *et al.* - RCT performed at 33 investigational sites across 10 countries, - 497 type 1 diabetes patients - 331 treated with detemir - 166 treated with NPH insulin Simulated cohort of 1,000 patients (at baseline) ; - Mean age (years) = 35 - 54.7% males - Average duration of diabetes = 13 years - Mean HbA1c = 8.3% - BMI = 24.7 kg/m^2
Intervention	Long-acting insulin analogues (Insulin detemir)
Comparison	NPH insulin
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of Insulin detemir with NPH:**
	• Undiscounted life expectancy [years, Mean (SD)];-
	  - Detemir = 22.32 (0.37)
	  - NPH = 22.02 (0.35)
	  - Difference = + 0.30 (0.51)
	• Life expectancy [years, Mean (SD)];-
	  - Detemir = 15.02 (0.19)
	  - NPH = 14.88 (0.18)
	  - Difference = + 0.14 (0.27)

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<td rowspan="1">Outcome measures/
Effect size (Con't)</td>
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- Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
  - Detemir = 8.35 (0.11)
  - NPH = 7.82 (0.10)
  - Difference = + 0.53 (0.15)

- Lifetime direct costs (SEK) [Mean (SD)];-
  - Detemir = 995,025 (19,580)
  - NPH = 968,881 (19,769)
  - Difference = + 26,144 (27,342)

- Total lifetime costs (SEK) (Direct + Indirect) [Mean (SD)];-
  - Detemir = 2,959,909 (64,727)
  - NPH = 3,040,022 (62,317)
  - Difference = - 80,113 (54,248)

Cost-effectiveness (from a healthcare payer perspective)

- Incremental cost-effectiveness ratio (ICER), based on life expectancy;-
  - SEK 190,208 per life year gained with detemir versus NPH

- ICER (based on quality-adjusted life expectancy);-
  - SEK 49,757 per QALY gained with detemir versus NPH

Incremental cost-effectiveness scatter plot and acceptability curve:-

- Assuming a willingness to pay thresholds of SEK 100,000 there was an 86.1% probability that detemir would be cost-effective versus NPH

- At willingness to pay thresholds of SEK 200,000, SEK 300,000 and SEK 400,000, the probability that detemir being cost-effective rose to 99.3%, 99.9% and 100.0%, respectively

Cost-effectiveness (from a societal perspective)

- ICER (based on life expectancy);-
  - detemir dominant

- ICER (based on quality-adjusted life life expectancy);-
  - detemir dominant

(Lifetime indirect costs with detemir treatment were SEK 106,257 lower than with NPH. These savings substantially offset the higher direct costs of SEK 26,144 making insulin detemir a dominant treatment over NPH from a societal perspective).

Sensitivity analysis

- Suggested that the base case results were most sensitive to variation in HBA1c and hypoglycaemic event rate benefits associated with insulin detemir.

- Reducing the benefit in HbA1c associated with insulin detemir to the value obtained with insulin NPH resulted in an ICER of SEK 78,190 per QALY gained. However, when capturing indirect costs, detemir treatment remained dominant.

- Assuming no benefits of detemir versus NPH treatment on the rate of major hypoglycaemic events, the ICER increased to SEK 119,711 per QALY gained. Adopting a societal perspective resulted in an ICER of SEK 58,142 per QALY gained for insulin detemir versus NPH.

Authors conclusion

Compared with NPH, insulin detemir is likely to be cost-effective from a healthcare payer perspective and dominant from a societal perspective in patients with type 1 diabetes in Sweden.

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<td>General comments</td>
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Quality assessment (CASP)

1. Yes
2. Yes
3. Yes
4. Yes
5. Yes
6. Yes
7. Cost, life expectancy, QALYs, ICER
8. Yes
9. Yes

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</table>

Evidence Table : **Economic**

Question : **Is insulin analogues cost-effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	2. Palmer AJ, Valentine WJ, Ray JA, Foos V, Lurati F, Smith I, Lammert M, Roze S. An economic assessment of analogue basal-bolus insulin versus human basal-bolus insulin in subjects with type 1diabetes in the UK. Current Medical Research and Opinion.2007; 23(4):895-901
Study Type / Methods	Economic evaluation The aim of this analysis was to compare the effects of insulin detemir plus insulin aspart compared with human insulin on long-term clinical and economic outcomes, in a cohort of type 1 diabetes patients in a UK cost setting. Health economic analysis was performed using the published and validated CORE Diabetes model which is Internet-based, interactive computer model designed to evaluate the long term health outcomes and economic consequences of interventions in type 1 and type 2 diabetes. Clinical and economic outcomes were calculated within the model using a non-parametric bootstrapping approach. This process simulates the lifetime progression of diabetes in 1000 hypothetical patients and repeats the process for each individual 1000 times. This produces 1000 mean values of clinical effectiveness and lifetime costs which can be used to generate the scatter plot diagram and acceptability curve to express the likelihood of a treatment being cost-effective over a comparator treatment. The findings from clinical trial report of Hermansen *et al.* were used as a basis for this analysis (improved glycaemic control, HbA1c -0.22%, P<0.001, reduced risk of hypoglycaemic events, -21%, P=0.036 and reduction of BMI, -0.30 kg/m2, P< 0.001 compared to a human basal-bolus regimen after 18 weeks. Probabilities of complications and HbA1c dependent adjustments were derived from major clinical and epidemiological studies. Complication and treatment costs were projected over patient lifetimes from a National Health Service perspective (2004). Costs and clinical benefits were discounted at 3.5% annually. The health state utilities used in the analysis were derived mainly from the UKPDS. A disutility of -0.0121 QALYs was applied for patients experiencing a major hypoglycaemic event and a disutility value of -0.0052 QALYs for all other hypoglycaemic events was applied. Sensitivity analyses were used to determine the effect of varying key assumptions on projected clinical and economic outcome. Changes in HbA1c levels, BMI and major rate of major hypoglycaemic events in response to treatments were investigated. Sensitivity analyses were also performed using discount rates of 6.0% for costs and 1.5% for clinical outcomes and on different time horizons.
LE	
Number of patients & Patient characteristics	Base case, Hermansen *et al.* - Multicentre, multinational, open-label, randomised parallel group trial - 595 type 1 diabetes patients - 298 treated with detemir and aspart - 197 treated with NPH and HSI - Age (years), mean (SD) = 39.1 years (13.2) - 63.2% males - Duration of diabetes (years), mean (SD) =15.3 years (10.3) - Mean HbA1c (%), mean (SD) = 8.83% (1.16) - BMI (kg/m^2), mean (SD) = 24.9 kg/m^2 (3.1)
Intervention	Insulin analogues (Insulin detemir plus insulin aspart)
Comparison	NPH insulin plus human soluble insulin (HSI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	Comparison of insulin detemir plus insulin aspart (analogue) versus human insulin (NPH and HSI): All costs and clinical outcomes were discounted at 3.5% per annum • Life expectancy [years, Mean (SD)];- - Analoque = 14.16 (0.16) - Human = 14.01 (0.16) - Difference = + 0.15 • Quality-adjusted life expectancy (years) [Mean (SD)];- - Analogue = 7.65 (0.09) - Human = 6.99 (0.08) - Difference = + 0.66 QALYs • Costs (£);- - Analogue = 40,876 (1,119) - Human = 39,222 (1,141) - Difference = 1,654 • ICER (based on life expectancy);- - £ 10,719 per life year gained • ICER (based on quality-adjusted life expectancy);- - £ 2,500 per QALY gained Costs of major hypoglycaemic events were reduced by £ 420 per patient. **Incremental cost-effectiveness scatter plot and acceptability curve:-** • A greater than 95% probability that analogue insulin would be regarded as cost-effective given a willingness-to-pay of £ 25,000 per QALY gained. • The sensitive part of the acceptability curve was around a willingness to pay threshold of £ 5,000 per QALY, which provided an 80% likelihood of analogue insulin being cost-effective compared to a human insulin basal-bolus regimen. **Sensitivity analyses:-** • Revealed that varying the effect of treatment on HbA1c had the greatest impact of ICER. When only the differenced in effects in HbA1c were considered, the ICER increased from £ 2,500 to £ 12,598 per QALY gained for analogue insulin versus human insulin. • When the cost of a major hypoglycaemic event was varied between £ 0 and £ 382, the ICER varied from £ 3,135 to £ 2,037 per QALY gained, respectively for analogue insulin versus human insulin. • When time horizons of 5, 10 and 25 years were used, costs per QALY decreased with increasing time horizon. With 5, 10 and 25-year time horizons, costs per QALY for analogue insulin versus human insulin were £ 2,937, £ 2,555 and £ 2,024 respectively. **Authors conclusion** Within the limitations of this modelling study, analogue basal-bolus therapy in type 1 diabetes patients can be considered 'good value for money' compared to human basal-bolus therapy in a UK setting.
General comments	assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy, QALYs, ICER 8. Yes 9. Yes

Evidence Table : **Economic**

Question : **Is long-acting insulin analogues cost-effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	3. Valentine WJ, Palmer AJ, Erny-Albrecht KM, Ray JA, Cobden D, Foos V, Lurati FM, Roze S. Cost-effectiveness of basal insulin from a US Health System Perspective: Comparative Analyses of Detemir, Glargine, and NPH.2006;23 (2) :191-207
Study Type / Methods	Economic evaluation The aim of this analysis was to compare in clinical and economic terms the long-acting insulin analogue detemir with intermediate-acting Neutral Protamine Hagedorn (NPH) insulin and with long-acting insulin glargine. Two separate analyses were undertaken and were included in the report. The first analysis modelled the impact of insulin detemir usage compared with NPH insulin. Data were extracted from an-18 week, open-label, randomised trial that compared treatment with twice-daily insulin detemir given in conjunction with mealtime insulin aspart versus treatment with twice daily NPH supplemented with human soluble insulin (Hermansen *et al.*) Through the CORE Diabetes Model, the short-term clinical effects of insulin detemir versus NPH were simulated over long-term horizon (35 years) from the US health system perspective. Simualtion cohort was based on 595 patients with type 1 diabetes (Hermansen *et al.*). The findings from clinical trial report of Hermansen *et al.* were used as a basis for this analysis (improved glycaemic control, HbA1c -0.22%, P< 0.001, reduced risk of hypoglycaemic events, -21%, P=0.036). Cost analyses from a societal perspective within the US health care system were performed, and both direct and indirect costs were taken into account. Direct costs, which were regarded as the sum of treatment, complication, and medication costs as listed by Medicare, were inflated to 2005 values. Indirect costs included those incurred through lost of productivity; these were based on US-specific data on average salaries, retirement age, and days of work missed because of complications. All costs and clinical benefits were discounted at an annual rate of 3.0%. A disutility of -0.0121 quality-adjusted life-years (QALYs) was applied for patients experiencing a major hypoglycaemic event and a disutility value of -0.0052 QALYs for all other hypoglycaemic events were applied. Sensitivity analysis was performed on key assumptions and variables used in the base case analysis; change in HbA1c, discount rate, duration of treatment effect, and costs for insulin and management of hypoglycaemia. Analysis was performed by means of a nonparametric bootstrapping approach.
LE	
Number of patients & Patient characteristics	BModel simulation population. detemir versus NPH:- - Mean age = 39 years - 63% males - Mean duration of diabetes (years) =15 years - BMI 9 (kg/m²), mean = 24.9 kg/m²
Intervention	Insulin analogues (Insulin detemir plus insulin aspart)
Comparison	NPH insulin plus human soluble insulin (HSI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin detemir versus NPH**
	
	• Undiscounted life expectancy [years, Mean (SD)];-
	  - Detemir = 21.346 (0.162)
	  - NPH = 21.026 (0.167)
	
	• Discounted life expectancy [years, Mean (SD)];-
	  - Detemir = 14.869 (0.162)
	  - NPH = 14.701 (0.167)
	  - Difference = + 0.168
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - Detemir = 8.018 (0.087)
	  - NPH = 7.32 (0.083)
	  - Difference = + 0.698
	
	• Direct medical costs (US$) [Mean (SD)];-
	  - Detemir = 118,746 (2,805)
	  - NPH = 108,295 (2,942)
	  - Difference = + 10,451
	
	• Indirect costs (US$) [Mean (SD)];-
	  - Detemir = 141,809 (5,034)
	  - NPH = 146,497 (5,214)
	  - Difference = - 4,688
	
	• Total lifetime costs (US$) [Mean (SD)];-
	  - Detemir = 260,555 (7,839)
	  - NPH = 254,792 (8,156)
	  - Difference = + 5763
	
	• ICER (based on quality-adjusted life expectancy);-
	  - US $ 14,974 per QALY gained with detemir versus NPH on the basis of direct costs
	
	Incremental cost-effectiveness scatter plot and acceptability curve:-
	
	• In the base case analysis, detemir based treatment was associated with a 100% likelihood that it would be cost-effective versus NPH, if the willingness to pay was $ 50,000 per QALY gained.
	
	Detemir versus NPH: diabetes related complications:-
	
	• Greater absolute reductions were projected for cumulative incidences of proliferative diabetic retinopathy, end-stage renal disease, microalbuminuria and gross proteinuria in the treatment with detemir compared with NPH, (% difference of 0.8%, 0.8%, 2.1% and 2.8% respectively).
	
	Sensitivity analyses:-
	
	• Most sensitive to changes in HbA1c levels. However, variation among any of the key assumptions, including HbA1c, did not alter the relative results.
	
	Authors conclusion
	
	Basal bolus therapy with detemir was projected to yield improvements in life expectancy and quality-adjusted life expectancy when compared with NPH. Detemir was also associated with a reduced cumulative incidence of diabetes-related complications and consequently represents a clinically and economically attractive treatment option from a societal and reimbursement perspective in the US setting.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy, QALYs, ICER 8. Yes 9. Yes

Evidence Table	**: Economic**
Question	**: Is insulin analogues cost-effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	4. Palmer AJ, Roze S, Valentine WJ, Smith I, Wittrup-Jensen U. Cost-effectiveness of detemir-based basal/bolus therapy for type 1 diabetes in a UK setting: an economic analysis based on meta-analysis results of four clinical trials. Current Medical Research and Opinion.2004; 20(11):1729-1746
Study Type / Methods	Economic evaluation A published, validated, peer-reviewed Markov simulation model (the CORE Diabetes Model) projected short-term results obtained from the weighted average of meta-analysis from four clinical trials (Hermansen *et al.*, Home *et al.*, Pieber *et al.*, Russel-Jones D *et al.*) to long-term incidence of complications, improvements in quality-adjusted life years (QALY), long-term costs and the cost-effectiveness for insulin detemir combinations versus NPH combinations in type 1 diabetes mellitus patients. Probabilities of complications and HbA1c –dependent adjustments were derived from the DCCT and other studies. Costs of treating complications in the UK were retrieved from published sources. Total direct costs (complications + treatment costs) for each arm were projected over patient lifetimes from a UK National Health Service perspective (2003). Both costs and clinical outcomes were discounted at 3.5% annually. The results of the meta-analysis showed that insulin detemir based basal/bolus treatment of type 1 diabetes led to improved HbA1c (0.15%-points lower), reduced risk of major hypoglycaemic events (by 2%) and reduction of BMI of 0.26 kg/m^2. A simulated cohort of patients was defined with baseline demographics, baseline complications and important concomitant medications that represented the combined study populations of the clinical trials from which the efficacy and safety results were derived. For major hypoglycaemic events, an event disutility of -0.0052 was used in the base case and sensitivity analysis was performed on this value. A lifetime horizon was used in the analysis. Sensitivity analyses were used to determine the effect of varying key assumptions on projected clinical and economic outcome. Changes in HbA1c levels, BMI and major rate of major hypoglycaemic events in response to treatments were investigated. Sensitivity analyses were performed using a range of discount rates between 0, 0% to 6.0% for costs and clinical outcomes and on different time horizons.
LE	
Number of patients & Patient characteristics	Baseline demographics of all patients from detemir studies used to define the cohort in the simulation:- Detemir combination:- - Age (years), mean (SD) = 40.2 years (12.5) - 61.6% males - Mean HbA1c(%), mean (SD) = 8.36% - BMI (kg/m^2) , mean (SD) = 25.1 kg/m^2 (3.3) NPH combination:- - Age (years), mean (SD) = 39.6 years (12.5) - 60.6% males - Mean HbA1c(%), mean (SD) = 8.36% - BMI (kg/m^2) , mean (SD) = 25.2 kg/m^2 (3.3)
Intervention	Insulin detemir only or insulin detemir plus insulin aspart
Comparison	NPH insulin only or plus HSI
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin detemir combination versus NPH combination**
	
	All costs and clinical outcomes were discounted at 3.5% per annum
	
	• Life expectancy [years, Mean (SD)];-
	  - Determir = 14.56 (0.16)
	  - NPH = 14.48 (0.17)
	  - Difference = + 0.08 (0.20)
	
	• Quality-adjusted life expectancy (years) [Mean (SD)];-
	  - Detemir = 9.77 (0.11)
	  - NPH = 9.68 (0.11)
	  - Difference = + 0.09 QALYs
	
	• Costs (£);-
	  - Detemir = 34,405 (953)
	  - NPH = 32,698 (1,007)
	  - Difference = 1,707(1,299)
	
	• ICER (based on life expectancy);-
	  - £ 22,474 per life year gained
	
	• ICER (based on quality-adjusted life expectancy);-
	  - £19,285 per QALYs gained
	
	Incremental cost-effectiveness scatter plot and acceptability curve:-
	
	• Under the base-case assumptions, detemir-based basal/bolus therapy had a 58% probability that it would be cost-effective, if the willingness-to-pay was £ 30,000.
	
	Detemir versus NPH: diabetes related complications:-
	
	• Due to better reduction from baseline of HbA1c, the development and progression of complications was delayed and the cumulative incidences of diabetic eye and renal disease, neuropathy, foot ulcers and amputations were decreased for detemir–based basal/bolus versus NPH-based basal/bolus therapy.
	
	Sensitivity analyses:-
	
	• Revealed that the differences in HbA1c had the greatest impact on the incremental cost-effectiveness ratio (ICER). When only the differences in effects of insulin detemir-based basal/bolus therapy on HbA1c were considered, the costs/QALY increased from £ 19,285 to £ 20,910 per QALY gained.
	
	• Varying the cost of a major hypoglycaemic event between £ 0 and £ 382 had only a minor effect on ICER (£ 19,968 and £ 18,787 per QALY gained respectively)
	
	Authors conclusion
	
	Short-term improvements seen with detemir combinations versus NPH combinations led to decrease complications, improvements in QALYs and reductions in complication costs, which partially offset the additional costs of detemir, leading to cost-effectiveness ratio which fell within a range considered to represent excellent value for money (< £ 35,000/QALY gained).

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy,QALYs, ICER 8. Yes 9. Yes

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Evidence Table	: **Economic**
Question	: **Is insulin analogues cost-effective for treatment of type 1 and type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	5. Cameron CG, Bennet HA. Cost- effectiveness of insulin analogues for diabetes mellitus. CMAJ.2009;180 (4):400-407
Study Type / Methods	Economic evaluation The aim of this analysis was to compare the cost-effectiveness of insulin analogues and conventional insulin used to treat type 1 and type 2 diabetes mellitus in adults. Center for Outcomes Research Diabetes Model which has been validated against published clinical and epidemiologic studies was used to calculate the cost-effectiveness estimates. Rapid-acting analogues (insulin aspart and insulin lispro) were compared with regular human insulin, and long-acting analogues (insulin glargine and insulin detemir) were compared with neutral protamine Hagedorn insulin. Clinical effects of therapy (HbA1c, mild to moderate and severe hypoglycaemia) required as inputs for the model was derived from meta-analyses of randomised controlled trials by the Canadian Agency for Drugs and Technologies in Health. The Canadian third-party payer such as a ministry of health or a single-payer insurance provider perspective was used, and therefore only included direct health care costs in the model (2007 Canadian dollars). A rate of discount of 5% was applied to both costs and outcomes. Utility estimates for the analysis was derived from a catalogue of EuroQoL-5D index scores for population of the United States. Time horizon of 60 years was used for patients with type 1 diabetes and 35 years for patients with type 2 diabetes. The effect of uncertainty across multiple model variables using nonparametric boot-strapping and second-order Monte Carlo simulations. One way sensitivity analysis was performed to examine the robustness of results to variation in parameters and model assumptions.
LE	
Number of patients & Patient characteristics	
Intervention	Short-acting insulin analogues and long acting insulin analogues
Comparison	Regular human insulin (RHI) and NPH insulin
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin analogues versus conventional human insulin**
	All costs and clinical outcomes were discounted at 5% per annum (2007 Canadian Dollars)
	
	a. Type 1 diabetes mellitus
	Insulin aspart versus regular human insulin
	
	• Costs ($);-
	  - Insulin Aspart = 71,551
	  - RHI = 72,171
	  - Difference = - 620
	
	• Quality-adjusted life-years:-
	  - Insulin Aspart = 11.016
	  - RHI = 10.961
	  - Difference = + 0.055
	
	• ICER per quality-adjusted life year gained, ($:)-
	  - Cost-saving

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Outcome measures/
Effect size (Con't)

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Insulin lispro versus regular human insulin

- Costs ($);-
  - Insulin lispro = 71,976
  - RHI = 71,794
  - Difference = + 182

- Quality-adjusted life years;-
  - Insulin lispro = 10.997
  - RHI = 10.991
  - Difference = + 0.006

- ICER per quality-adjusted life year gained ($);-
  - $ 28,996

Insulin glargine versus NPH insulin

- Costs ($);-
  - Insulin glargine = 70,751
  - NPH insulin = 67,328
  - Difference = + 3,423

- Quality-adjusted life years;-
  - Insulin glargine = 11,136
  - NPH insulin = 11,097
  - Difference = + 0.039

- ICER per quality-adjusted life year gained ($);-
  - $ 87,932

Insulin detemir versus NPH insulin

- Costs ($);-
  - Insulin detemir = 72,714
  - NPH insulin = 68,370
  - Difference = + 4,344

- Quality-adjusted life years;-
  - Insulin detemir = 11,045
  - NPH insulin = 11,034
  - Difference = + 0.011

- ICER per quality-adjusted life year gained ($);-
  - $ 387,729

Incremental cost-effectiveness scatter plot and acceptability curve:-

- At a cost-effectiveness threshold of Can$ 50,000 per quality-adjusted life-year, the probability that each insulin analogues was more cost effective than conventional insulin was 68.8% for insulin aspart, 51.2% for insulin lispro, 42.5% for insulin glargine and 29.2% for insulin detemir.

- When fear of hypoglycaemia was incorporated as a complication in the model, results from sensitivity analyses showed that insulin aspart remained cost-saving when compared with conventional insulin. However, the ICER per quality-adjusted life year decreased to Can $1,117 for insulin lispro, Can$ 17,225 for insulin glargine and Can$ 25,666 for insulin detemir.

- When no difference in HbA1c between treatment comparators was assumed, ICER increased to Can$ 104,598 for insulin aspart, Can$ 673,041 for insulin lispro, Can$ 916,401 for insulin glargine and Can$ 1,958,928 for insulin detemir.

b. Type 2 diabetes mellitus

Insulin aspart versus regular human insulin

- Costs ($);-
  - Insulin Aspart = 63,792
  - RHI = 63,459
  - Difference = + 333

- Quality-adjusted life-years:-
  - Insulin Aspart = 5.899
  - RHI = 5.884
  - Difference = + 0.015

- ICER per quality-adjusted life year gained, ($):-
  - $ 22,488

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Outcome measures/ Effect size (Con't)	**Insulin lispro versus regular human insulin** • Costs ($);- - Insulin lispro = 66,274 - RHI = 65,490 - Difference = + 784 • Quality-adjusted life years;- - Insulin lispro = 5.773 - RHI = 5.767 - Difference = + 0.006 • ICER per quality-adjusted life year gained ($);- - $ 130,865 **Insulin glargine versus NPH insulin** • Costs ($);- - Insulin glargine = 67,132 - NPH insulin = 62,187 - Difference = + 4,945 • Quality-adjusted life years;- - Insulin glargine = 5,806 - NPH insulin = 5,798 - Difference = + 0.008 • ICER per quality-adjusted life year gained ($);- - $ 642,994 **Insulin detemir versus NPH insulin** • Costs ($);- - Insulin detemir = 65,749 - NPH insulin = 59,228 - Difference = + 6,521 • Quality-adjusted life years;- - Insulin detemir = 5,944 - NPH insulin = 5,978 - Difference= - 0.034 • ICER per quality-adjusted life year gained ($);- - Dominated by conventional insulin **Incremental cost-effectiveness scatter plot and acceptability curve:-** • At a cost-effectiveness threshold of Can$ 50,000 per quality-adjusted life-year, the probability that each insulin analogue was more cost effective than conventional insulin was 52.3% for insulin aspart, 46.3% for insulin lispro, 25.1% for insulin glargine and 10.8% for insulin detemir. • When fear of hypoglycaemia was incorporated as a complication in the model, results from sensitivity analyses showed that the ICER per quality-adjusted life year decreased to Can$ 4,429 for insulin aspart, Can$ 12,115 for insulin lispro, Can$ 73,989 for insulin glargine and Can$ 234,606 for insulin detemir. • When no difference in HbA1c between treatment comparators was assumed, ICER increased to Can$ 543,584 for insulin aspart, Can$ 80,445 for insulin lispro, Can$ 1,577,457 for insulin glargine and Can$ 882,155 for insulin detemir **Authors conclusion** The cost-effectiveness of insulin analogues depend on the type of insulin analogue and whether the patient receiving the treatment has type 1 or type 2 diabetes. With the exception of rapid-acting insulin analogues in type 1 diabetes, routine use of insulin analogues, especially long acting analogues in type 2 diabetes is unlikely to represent an efficient use of finite healthcare resources.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy, QALYs, ICER 8. Yes 9. Yes

Evidence Table : **Economic**

Question : **Is insulin analogues cost-effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	6. Brandle M, Azoulay M, Geiner A. Cost-effectiveness of insulin glargine versus NPH insulin for treatment of Type 2 diabetes mellitus, modelling the interaction between hypoglycaemia and glycaemic control in Switzerland. International journal of Clinical Pharmacology and Therapeutics. 2011;49(3):217-230
Study Type / Methods	Economic evaluation The aim of this study was to evaluate short-term and long-term clinical and economic outcomes associated with insulin glargine or NPH insulin in patients with type 2 diabetes mellitus inadequately controlled with oral-anti-diabetic drugs in Switzerland, modelling the interaction between hypoglycaemia and glycaemic control (HbA1c). A validated discrete event simulation (DES) model for type 2 diabetes mellitus was used to predict incidence of short-term complications (symptomatic, nocturnal and severe hypoglycaemic events) and long-term complications (microvascular and macrovascular events), life expectancy, quality-adjusted life years (QALYs) and direct medical costs in patients treated with insulin glargine or NPH insulin. The model was populated with published Swiss patient characteristics with type 2 diabetes mellitus. Baseline risks of hypoglycaemic events, utility decrements of diabetes diabetes- related long-term complications and hypoglycaemia fear score were derived from the literature. Relative risk reductions of hypoglycaemia adjusted for HbA1c using insulin glargine compared with NPH insulin were based on a published negative binomial meta-regression analysis. Costs of severe hypoglycaemia, micro-and macrovascular events were analyzed from literature whenever possible otherwise guideline-projected resource-use estimations were valued with Swiss official prices or tariffs in 2006 CHF. Simulations were run with 1,000 patients per cohort over a time horizon of 40 years. Incremental cost-effectiveness ratio (ICERs) was presented as cost per QALY and per life year gained (LYG). Future costs and clinical benefits were discounted at 3.5%.
LE	
Number of patients & Patient characteristics	Baseline characteristics of type 2 patients for base-case analysis :-. - Mean age (years) = 66 ± 12.3 years - 49.4% males - Duration of diabetes (years) = 9.2 years ± 7.04 - Mean HbA1c(%), mean (SD) = 9.4% (2.10) - Weight (kg) = 81.2 kg ± 16.55 - HbA1c (99.0%) = 9.0%
Intervention	Insulin glargine
Comparison	NPH insulin
Length of follow up (if applicable)	

| Outcome measures/ Effect size | **Comparison of insulin glargine versus NPH insulin:-**

All costs and clinical outcomes were discounted at 3.5% per annum

• Life expectancy (years) Mean;-
  - Glargine = 14.897
  - NPH = 14.847
  - Difference = + 0.050

• Quality-adjusted life expectancy (QALYs) Mean;-
  - Glargine = 10.207
  - NPH = 10.109
  - Difference = + 0.098

• Total direct costs (CHF);-
  - Glargine = 62,691
  - RHI = 60,113
  - Difference = CHF 2,578

• ICER per life year gained (CHF);-
  - CHF 51,100

• ICER per QALY gained (CHF);-
  - CHF 26,271

Incremental cost-effectiveness scatter plot and acceptability curve:-

• Giving a willingness to pay threshold of CHF 60,000 per QALY insulin glargine can be considered as a cost-effective strategy compared with NPH insulin.

Sensitivity analyses:-

• The ICER varied within reasonable limits. The majority of the mean ICER values were within the willingness to pay threshold of CHF 60,000 per QALY. Decreasing the hypoglycaemia risk reduction by 50% was the sole exception, which generated an ICER of CHF 62,442 per QALY gained somewhat above this threshold. Even when assuming 0% HbA1c reduction, the ICER remained substantially below this threshold and reached CHF 45,376 per QALY gained.

Authors conclusion

This study evaluated, for the first time, the cost-effectiveness of insulin glargine versus NPH insulin for treatment of type 2 diabetes mellitus considering the interaction between glycaemic control and hypoglycaemia in Switzerland. The base case and sensitivity analyses demonstrated that insulin glargine proved to be cost-effective with respect to accepted willingness to pay threshold and therefore represents good value for money. |
| **General comments** | Quality assessment (CASP)

1. Yes

2. Yes

3. Yes

4. Yes

5. Yes

6. Yes

7. Cost, life expectancy QALYs, ICER

8. Yes

9. Yes |

Evidence Table : **Economic**

Question : **Is insulin analogues cost-effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	7. Brandle M, Azoulay M, Geiner A. Cost-effectiveness and cost-utility of insulin glargine compared with NPH insulin based on a 10-year simulation of long-term complications with the Diabetes Mellitus Model in patients with type 2 in Switzerland. International journal of Clinical Pharmacology and Therapeutics. 2007;45(4):203-220
Study Type / Methods	Economic evaluation The aim of this study was to evaluate the cost-effectiveness of insulin glargine compared with NPH insulin in patients with type 2 diabetes and in whom oral anti-diabetics had failed in Switzerland. Long-term diabetes outcomes were simulated with the Diabetes Mellitus Model (DMM) over a period of 10 years. The incidences of long-term complications (micro-and macrovascular events) were simulated for 10,000 patients over 10 years for six different scenarios. The scenarios were based on HbA1c reductions observed in clinical trials (Fritsche *et al.*) For insulin glargine, HbA1c reduction of 0.96% (pessimistic case) and 1.24% (optimistic case) were simulated for three different HbA1c baseline values (10, 9 and 8%). For NPH insulin the HbA1c was assumed to be 0.84%. A cost model and a utility model were developed in order to use the cumulated incidences of the simulations for the calculation of cost and QALYs. The unit costs of micro-and macrovascular events were assessed by a combination of cumulated incidences in each event up to 10 years with the corresponding unit cost per event (in addition to the acquisition cost) or with disutility values per event, respectively. Events, total cost, and QALYs were discounted at 3%. In scenarios where no savings could be shown for insulin glargine, incremental cost-effectiveness ratios (ICER) were calculated as the incremental cost per QALY gained. Sensitivity analysis was performed on the discount rates used in the analysis and on the level of baseline HbA1c at the start of the simulation using a range between 8% and 10%.
LE	
Number of patients & Patient characteristics	Baseline characteristics of all cohorts:-. - Mean age (years, mean ± SD) = 66 ± 12.3 years - 50.1% women - Duration of diabetes (years, mean ± SD)) = 9.0 years ± 7.0 - Mean HbA1c(%), mean (SD) = 9.4% (2.10) - BMI (kg/m², mean ± SD) = 29.4 kg ± 5.5 - Patients with hypertension (%) = 38%
Intervention	Insulin glargine
Comparison	NPH insulin
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Cost-effectiveness of insulin glargine compared with insulin, NPH insulin, 3.0% discount rate per annum**
	
	a. Pessimistic case scenarios (Change in HbA1c = -0.12%)
	
	• **Baseline HbA1c (10%)**
	  - Incremental cost = CHF 1,532
	  - Total prevented events = 0.06
	  - Cost per prevented event = CHF 27,742
	  - QALYs gained = 0.038
	  - Costs per QALY gained = CHF 40,441

Outcome measures/ Effect size (Con't)	• **Baseline HbA1c (9%)**
	  - Incremental cost = CHF 1,685
	  - Total prevented events = 0.05
	  - Cost per prevented event = CHF 32,451
	  - QALYs gained = 0.037
	  - Costs per QALY gained = CHF 45,701
	
	• **Baseline HbA1c (8%)**
	  - Incremental cost = CHF 1,887
	  - Total prevented events = 0.05
	  - Cost per prevented event = CHF 41,620
	  - QALYs gained = 0.038
	  - Costs per QALY gained = CHF 49,468
	
	b. Optimistic case scenarios (Change in HbA1c = - 0.40%)
	
	• **Baseline HbA1c (10%)**
	  - Incremental cost = CHF -95
	  - Total prevented events = 0.18
	  - Cost per prevented event = galrgine dominant
	  - QALYs gained = 0.123
	  - Costs per QALY gained = glargine dominant
	
	• **Baseline HbA1c (9%)**
	  - Incremental cost = CHF 350
	  - Total prevented events = 0.17
	  - Cost per prevented event = CHF 2,054
	  - QALYs gained = 0.123
	  - Costs per QALY gained = CHF 2,853
	
	• **Baseline HbA1c (8%)**
	  - Incremental cost = CHF 734
	  - Total prevented events = 0.15
	  - Cost per prevented event = CHF 4,899
	  - QALYs gained = 0.128
	  - Costs per QALY gained = CHF 5,711
	
	Sensitivity analyses:-
	
	• Sensitivity analysis using discount rates of 0% and 5% annually for both clinical and cost outcomes had no big impact on the relative results.
	
	Authors conclusion
	
	The 10 year simulations demonstrated that improved HbA1c levels with insulin glargine versus NPH insulin are associated with a reduction of long-term complications, mortality and associated costs. Achieving HbA1c reductions of 0.4 and 0.12%, insulin glargine led to an improved quality of life and represents good to excellent value for money compared with NPH insulin in Switzerland.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy QALYs, ICER 8. Yes 9. Yes

Evidence Table	: **Economic**
Question	: **Is insulin analogues cost-effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	8. McEwan P, Poole CD, Tetlow T, Holmes P, Currie CJ. Evaluation of the cost-effectiveness of insulin glargine verus NPH insulin for the treatment of type 2 diabetes in the UK. Current Medical research and Opinion.2007;239(1):S21-S31
Study Type / Methods	Economic evaluation The aim of this study was to evaluate the relative cost-effectiveness of glargine versus NPH insulin using pooled data from clinical trials in people with type 2 diabetes in the UK. The evaluation was undertaken within the context of the UK National Health service (NHS) and used the NHS perspective. The method used was a cost-utility analysis (CUA) intended to determine the cost per quality-adjusted life year gained (QALY gained) using glargine versus NPH insulin. The study used a discrete event simulation (DES) model designed to forecast the costs and health outcome of a cohort of 1000 subjects over 40 years. The two main scenarios involved a difference in the likelihood of hypoglycaemia or a difference in HbA1c. Prices were in UK £2005 costs. Costs and benefit were discounted at 3.5% per year. Effectiveness data were pooled from randomised clinical trials (Rosenstock *et al.*, MRM meta-analysis). Utility estimates were derived from the UKPDS study or generated via the HODaR database. One-way sensitivity analysis was carried out on all key model inputs.
LE	
Number of patients & Patient characteristics	Base-case baseline patient characteristics:-. - Age (years) = 58 years - 52% male - Weight (kg) = 81 kg - Mean HbA1c (%), mean (SD) = 9.0% - Total cholesterol (mmol/L) = 5.2 - HDL (mmol/L) = 1.04 - Systolic blood pressure = 141
Intervention	Insulin glargine
Comparison	NPH insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Comparison of insulin glargine versus NPH insulin:-** **All costs and clinical outcomes were discounted at 3.5% per annum** • Under the hypoglycaemia scenario the mean incremental cost-effectiveness ratio (ICER) was £ 10,027 per QALY gained. • Under the HbA1c scenario, the mean ICER was £ 13,921 per QALY gained **Sensitivity analyses:-** • In detailed one-way sensitivity analysis intended to investigate the effects of uncertainty, the ICER varied within reasonable limits and the majority of the mean ICER values were within £ 20,000 per QALY gained and all scenarios were within £ 30,000 per QALY. Reducing the hypoglycaemia risk and HbA1c treatment effects by 50% resulted in cost per QALY of £ 29,040 and £ 22,420 respectively. **Authors conclusion** Insulin glargine resulted in significant health benefits and represents excellent value for money for the treatment of type 2 diabetes in the UK.
General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy QALYs, ICER 8. Yes 9. Yes

Evidence Table	**: Economic**
Question	**: Is insulin analogues cost-effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	9. Palmer JL, Gibbs M, Sheijbeler H WKFH, Nielsen S, Kotchie RW, Nielsen S, White J, Valentine WJ. Cost-effectiveness of switching to biphasic insulin aspart in poorly controlled type 2 diabetes patients in China. Adv Ther. 2008;25 (8):752-774
Study Type / Methods	Economic evaluation The aim of this analysis was to evaluate the long-term cost and clinical outcomes associated with switching poorly controlled type 2 diabetes patients group in China to BIAsp 30 from BHI, based on results from PRESENT. A published and validated computer simulation model of diabetes (CORE diabetes model) was used to assess the cost-effectiveness of BIAsp 30 in Chinese type 2 diabetes patients. Treatment effects for BIAsp 30 were derived from PRESENT. The Physicians Routine Evaluation of Safety and Efficacy of NovoMix 30 Therapy (PRESENT) study was an open-label, multi-country, single-arm, observational study that enrolled over 20,000 patients with type 2 diabetes. Data from the subset of patients transferred to BIAsp 30 from biphasic human insulin in China (n=2,289) were analysed where significant improvements in glycosylated haemoglobin (HbA1c) levels (-1.82% P<0.001) and substantial reductions in hypoglycaemic events [-1100 events (major and minor) per 100 patients years, P<0.001] were observed in poorly controlled patients (baseline HbA1c=8.81%) over 3 months. The baseline characteristics and risk factors of the simulated cohort were based on those of the Chinese subgroup of PRESENT. The analysis was undertaken from the perspective of a third-party payer (managed care organizations, insurance companies, etc) incorporating future treatment costs, patient management costs and medical complication costs. The costs of lost working time due to illness and death prior to the retirement age were excluded. All costs were presented in and calculated in 2007 Chinese Yuan (CNY). Primary research was performed by the authors to obtain data for diabetes related complication and management costs and practices in China. A disutility of -0.0035 was applied for each minor hypoglycaemic event and a disutility value of -0.0118 was applied for major hypoglycaemia. In the base case analysis, both costs and clinical outcomes were discounted at the rate of 3% per annum, The time horizon was set to 30 years. Several one-way sensitivity analysis were performed to assess the effect of varying key model parameters on final outcomes. A simulated cohort of 1000 patients was run through the model 1000 times for each simulation with mean values and standard deviations generated using a non-parametric bootstrapping approach.
LE	
Number of patients & Patient characteristics	Baseline characteristics of patients in the simulated cohort:-. - Mean age (years, mean (SD) = 56.7 (11.2) years - 57.6% male - Mean duration of diabetes (years) mean (SD)) = 6.6 years (4.9) - Mean HbA1c (%), mean (SD) = 8.8% (1.6) - BMI (kg/m2), mean (SD) = 24.3 kg (2.6) - Systolic blood pressure (mmHg), Mean (SD)=137.7 mmHg (22.6)
Intervention	BIAsp 30
Comparison	BHI 30
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin BIAsp 30 versus BHI 30:-**
	
	All costs and clinical outcomes were discounted at 3.0% per annum
	
	• Discounted life expectancy [years, Mean (SD)];-
	  - BIAsp 30 = 9.91 (0.18)
	  - BHI 30 = 9.53 (0.18)
	  - Difference = + 0.38
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - BIAsp 30 = 6.32 (0.12)
	  - BHI 30 = 5.41 (0.11)
	  - Difference = + 0.91
	
	• Total costs, (CNY);-
	  - BIAsp 30 = 203,126 (4,644)
	  - BHI 30 = 201,376 (5,252)
	  - Difference = 1,751
	
	• ICER for BIAsp 30 based on life expectancy;-
	  - CNY 4,654 per life year gained
	
	• ICER for BIAsp 30 based on quality-adjusted life expectancy;-
	  - CNY 1,926 per QALY gained
	
	Incremental cost-effectiveness scatter plot and acceptability curve:-
	
	• At a hypothetical willingness to pay threshold of CNY 100,000, BIAsp 30 had a 100% likelihood of being considered cost-effective from a third-party payer perspective.
	
	Sensitivity analyses:-
	
	• Sensitivity analysis revealed that modelled outcomes were most sensitive to changes in treatment effects, time horizons and complication costs.
	
	• When the diabetes-related complications and management costs applied in the model were increased by 20% from base case, BIAsp 30 was associated with cost savings of CNY 1,652 per patient. When these cost were reduced by 20% from base case, BIAsp 30 was associated with increased direct costs of CNY 4,889 per patient.
	
	• When five sensitivity analyses were performed using a range of HbA1c reductions for BIAsp 30 (from the -1.82%-points reduction observed in PRESENT to 0% calculated in a Cochrane review of RCTs of insulin analogues). ICERs remained below the willingness to pay threshold used in this analysis of CNY 100,000 per QALY gained.
	
	• When no reduction in hypoglycaemic events was modelled for BIAsp 30, it was associated with increased incremental costs of CNY 5,388 per patient versus BHI.
	
	Cumulative incidence of diabetes-related complications
	
	• Patients treated with BIAsp 30 had a reduced cumulative incidence of most diabetes-related complications compared with patients treated with BHI; end stage renal disease (35% risk reduction), eye complications (36% risk reduction in the incidence of proliferative retinopathy), congestive heart failure (8% risk reduction) and myocardial infarction (16% risk reduction).
	
	Authors conclusion
	
	BIAsp 30 was projected to substantially improve clinical outcomes but associated with increased lifetime medical costs. BIAsp 30 would be considered cost-effective in China given a willingness- to-pay threshold of CNY 100,000 per QALY gained in type 2 diabetes patients poorly controlled on BHI.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes, but observational study 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy QALYs, ICER 8. Yes 9. Yes

Evidence Table	**: Economic**
Question	**: Is insulin analogues cost-effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	10. Palmer JL, Knudsen MS, Aagren M, Thomsen TL. Cost-effectiveness of switching to biphasic insulin aspart from human premix insulin in a US setting. Journal of Medical Economics. 2010;13(2):212-220
Study Type / Methods	Economic evaluation The aim of this study was to evaluate the cost-effectiveness of switching to biphasic insulin aspart (BIAsp 30) from human premix insulin for type 2 diabetes in the United States (US) setting. The previously published and validated IMS Core Diabetes Model was used to project life expectancy, quality-adjusted life expectancy (QALE) and costs over 30 years. Patient characteristics and treatment effects were based on 311 patients included in the Canadian arm of IMPROVE observational study. IMPROVE is a large, single arm, 26-week, observational study conducted in 11 countries looking into the safety and efficacy of BIAsp 30 when used in routine clinical settings among patients with varying duration of type 2 diabetes and complication status. Mean Hb1c was 8.4%, duration of diabetes 16 years and prevalence of complications was high at baseline. Based on results from IMPROVE, treatment with BIAsp 30 was associated with a change in HbA1c of −0.58% points. The occurrence of major hypoglycaemia was reduced from 30.9 events per 100 patient-years (baseline events rate with BHI 30) to 7,7 events per 100 patients-years. Switching to BIAsp 30 was associated with moderate weight gain; an increase in BMI by 0.28 kg/m^2 relative to baseline. The study was conducted from the perspective of a third-party healthcare payer in the US setting. Direct costs comprised the sum of treatment, complication and medications costs as derived from published sources and were inflated to year 2008. Future clinical and cost outcomes were discounted at the rate of 3% per annum. Health state utilities for type 2 diabetes and its complications were derived whenever possible from UKPDS supplemented with data from other published sources. Disutility values for major and minor hypoglycaemic events were -0.0118 and -0.0035, respectively. The impact of key assumptions made for base case analysis was assessed in sensitivity analysis. Monte Carlo simulation techniques were used to calculate cost-effectiveness outcomes. A cohort of 1000 patients was run through the model 1000 times for each simulation with mean values and standard deviations generated using a non-parametric bootstrapping approach.
LE	
Number of patients & Patient characteristics	Baseline characteristics of patients in the simulated cohort:-. - Mean age (years) mean (SD) = 64.2 (11.0) years - 62.0% male - Mean duration of diabetes (years) mean (SD)) = 16.4 years (8.9) - Mean HbA1c (%), mean (SD) = 8.4% (2.10) - BMI (kg/m^2), mean (SD) = 32.1 kg (6.7) - Systolic blood pressure (mmHg), Mean (SD) = 136.4 mmHg (17.1)
Intervention	BIAsp 30
Comparison	BHI 30
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin BIAsp 30 versus BHI 30:-**
	
	All costs and clinical outcomes were discounted at 3.0% per annum
	
	• Undiscounted life expectancy [years, Mean (SD)];-
	  - BIAsp 30 = 9.537 (0.232)
	  - BHI 30 = 9.335 (0.239)
	  - Difference = + 0.202
	
	• Discounted life expectancy [years, Mean (SD)];-
	  - BIAsp 30 = 7.597 (0.161)
	  - BHI 30 = 7.473 (0.169)
	  - Difference = + 0.124
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - BIAsp 30 = 4.605 (0.101)
	  - BHI 30 = 4.304 (0.101)
	  - Difference = + 0.301
	
	• Direct medical costs ($);-
	  - BIAsp 30 = 76,517 (2,359)
	  - BHI 30 = 67,518 (2,375)
	  - Difference = 8,998
	
	• ICER;-
	  - USD 29,870 per QALY gained
	
	Incremental cost-effectiveness scatter plot and acceptability curve:-
	
	• At a willingness-to-pay threshold of $50,000 per QALY gained, BIAsp 30 had an 84% likelihood of being considered cost-effective to BHI 30.
	
	Sensitivity analyses:-
	
	• Sensitivity analysis revealed that projected outcomes were most sensitive to changes in HbA1c and hypoglycaemia event rates.
	
	• When the BIAsp 30 associated change in HbA1c was set to 50% of that observed in the Canadian BHI 30 cohort the ICER increased moderately $38,767 per QALY gained. When no reduction in HbA1c was assumed ICER increased to $58,462 per QALY gained.
	
	• When the reduction in major hypoglycaemia was assumed as 11.6 events per 100 patient-years (versus 23.2 events per 100 patients-years in the base case) the ICER for BIAsp 30 was $48,396 per QALY gained. When no reduction in hypoglycaemia was assumed for BIAsp 30 an ICER of $95,819 per QALY gained was calculated for BIAsp 30.
	
	Cumulative incidence of diabetes-related complications
	
	• Over patient lifetimes treatment with BIAsp 30 was associated with a lower cumulative incidence of most diabetes-related complications; end stage renal disease (0.83 versus 1.55%), peripheral vascular disease (10.34 versus 12.82%), severe vision loss (5.44 versus 6.67%) compared to BHI 30.
	
	Authors conclusion
	
	BIAsp 30 may represent a cost-effective treatment option in the US setting for advanced type 2 diabetes experiencing poor glycaemic control or hypoglycaemia on human premix insulin.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes, but observational study 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy QALYs, ICER 8. Yes 9. Yes

Evidence Table : **Economic**

Question : **Is insulin analogues cost-effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	11. Lee KH, Seo SJ, Smith-Palmer J, Palmer JL, White J, Valentine WJ. Cost-effectiveness of switching to Biphasic Insulin Aspart 30 from human insulin in patients with poorly controlled type 2 diabetes in South Korea. Value in Health. 2009;25 (S3):S55-S61
Study Type / Methods	Economic evaluation The aim of this analysis was to estimate the long-term clinical and cost outcomes associated with switching patients poorly controlled ton HI to BIAsp 30 in South Korea based on the data from the PRESENT study. A published and validated diabetes computer simulation model (the IMS CORE diabetes model) was used to evaluate the long-term clinical and economic outcomes associated with switching to BIAsp 30, using treatment effects from the South Korean subgroup of the Physician's Routine Evaluation of Safety and efficacy of NovoMix 30 Therapy (PRESENT) study (n=1,311) and cost data collected through primary research. Results from a subgroup analysis of the South Korean PRESENT study showed that at 6 months after switching to BIAsp 30 treatment, HbA1c was reduced by 0.82% points (P<0.001) from baseline. All Hypoglycaemic events (major and minor) wetre reduced from 494 to 188 events per 100 patients years (P< 0.001), The baseline demographics, characteristics, risk factors and comorbidities were derived from the South Korean PRESENT subgroup and from published studies in comparable populations where necessary. A third-party payer perspective was adopted for the analysis, incorporating the direct costs of treatment, patient management and diabetes-related l complication costs. All costs were accounted in and calculated in 2007 South Korean Won (KRW; US$1 = KRW 936.53). In base-case analysis, future costs and clinical benefits were discounted at a rate of 5% per annum, in accordance with Korean Health Insurance Review Agency guidelines. Analysis was performed over a time horizon of 30 years. A series of sensitivity analysis were performed to address the impact of several key parameters on final outcome. A simulated cohort of 1000 patients was run through the model 1000 times for each simulation with mean values and standard deviations generated using a non-parametric bootstrapping approach.
LE	
Number of patients & Patient characteristics	Baseline patients demographics:-. - Mean age (years) mean (SD) = 57.93 (13.64) years - 45.7% male - Duration of diabetes (years) mean (SD)) = 11.02 years (7.17) - Mean HbA1c (%), mean (SD) = 8.82% (1.61) - BMI (kg/m²), mean (SD) = 24.57 kg (3.21) - Systolic blood pressure (mmHg), Mean (SD) = 139.1 mmHg (21.9)
Intervention	BIAsp 30
Comparison	BHI 30
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin BIAsp 30 versus BHI 30:-**
	
	All costs and clinical outcomes were discounted at 5.0% per annum
	
	• Life expectancy [years, Mean (SD)];-
	  - BIAsp 30 = 8.62 (0.13)
	  - BHI 30 = 8.47 (0.13)
	  - Difference = + 0.15 (0.18)
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - BIAsp 30 = 5.68 (0.09)
	  - BHI 30 = 5.38 (0.09)
	  - Difference = + 0.30 (0.12)
	
	• Total costs, (KRW);-
	  - BIAsp 30 = 12,214,835 (259,424)
	  - BHI 30 = 10,437,982 (253,378)
	  - Difference = 1,776,855 (358,623)
	
	• ICER for BIAsp 30 based on quality-adjusted life expectancy;-
	  - KRW 5,915,198 per QALY gained.
	
	Incremental cost-effectiveness scatter plot and acceptability curve:-
	
	• Assuming a willingness-to-pay threshold of KRW 25 million per QALY gained (less than gross domestic product per capita on a purchasing power parity basis), there is a 97.5% chance BIAsp 30 will be cost-effective compared with HI.
	
	Sensitivity analyses:-
	
	• The outcomes of the simulations were most sensitive to alterations in projected efficacy.
	
	• Assuming that BIAsp 30 treatment resulted in no improvement in hypoglycaemic events, the ICER increased to KRW19,248,486.
	
	• If the improvement in terms of the projected reduction in HbA1c was halved or no reduction at all was projected, the ICER for BIAsp 30 was KRW 8,037,980 per QALY gained and KRW 11,911,421 per QALY gained.
	
	Cumulative incidence of diabetes-related complications
	
	• BIAsp 30 reduced the overall incidence of neuropathy and renal, cardiovascular, ophthalmologic, and diabetic complications. Neuropathy reduction by 3.54% and gross proteinuria by 2.86%.
	
	Authors conclusion
	
	Switching patients uncontrolled on HI to BIAsp 30 was projected to improve life expectancy and quality adjusted life expectancy. Suggest that BIAsp 30 could be cost-effective treatment option in type 2 diabetes patients poorly controlled on HI in South Korea.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes, but observational study 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy, QALYs, ICER 8. Yes 9. Yes

Evidence Table	**: Economic**
Question	**: Is insulin analogues cost-effective for treatment of type 2 diabetes mellitus compared to human insulin?**

Bibliographic citation	12. Palmer JL, Gordon G, Nielsen S, Kotchie RW, Valentine WJ, Palmer AJ, Roze S. Cost-effectiveness of insulin aspart versus human soluble insulin in type 2 diabetes in four European countries: subgroup analyses from PREDICTIVE study. Current Medical Research and Opinion. 2008; 24(5):1417-1428
Study Type / Methods	Economic evaluation The aim of this study was to evaluate the long-term economic and clinical implications of insulin Aspart (IAsp) treatment for type 2 diabetes in Sweden, Spain, Italy and Poland compared to human insulin based on the PREDICTIVE study. A published and validated diabetes computer simulation model (the IMS CORE diabetes model) was used to evaluate the long-term clinical and economic outcomes associated with IAsp treatment with and without concurrent oral antidiabetic (OAD) usage in type 2 diabetes patients in the Swedish, Spanish, Italian, and Polish settings. Treatment effects for IAsp were taken from the European sub-set of PREDICTIVE study, where both both treatments were associated with reductions in HbA1c and BMI. Patients who received insulin therapy only and those prescribed OADs in addition to insulin were included in the analysis. In PREDICTIVE, patients on IAsp benefited from greater reductions in HbA1c (-0.93% versus -0.55%) and BMI (-0.18 kg/m^2 versus -0.03 kg/m^2) compared with human soluble insulin. A cohort was defined for each country setting, with baseline age, duration of diabetes and HbA1c based on PREDICTIVE data. Both societal and third-party payer perspectives were used for the Swedish analysis. Direct medical costs only were accounted in the Spanish, Italian and Polish settings. Direct medical costs were accounted in 2005 Swedish Kroner for Sweden and 2006 euros for Spain, Italy and Poland. Costs associated with treatment of diabetes-related complications were obtained from country specific published sources. For the Swedish base-case analysis, a discount rate of 3%per annum was applied for future costs and clinical benefits as recommended by the Swedish Pharmaceutical Benefits Board. Discount rates for both costs and clinical benefits of 6%, 3% and 5% per annum were used in the Spanish, Italian and polish analyses, respectively. The time horizon was set to 35 years for all countries in the base case analysis. Several one-way sensitivity analyses were performed to assess the effect of varying key parameters on costs and outcomes. A simulated cohort of 1000 patients was run through the model 1000 times for each simulation with mean values and standard deviations generated using a non-parametric bootstrapping approach.
LE	
Number of patients & Patient characteristics	Baseline cohort characteristics:-. - Mean age (years) = 61.6 years - 45.7% male - Duration of diabetes (years) mean = 13.2 years - Mean HbA1c (%), = 8.2% - BMI (kg/m^2), mean = 29.8 kg (3.21)
Intervention	Insulin Aspart (IAsp)
Comparison	Human soluble insulin (HI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin Aspart versus Human soluble insulin:-**
	
	Sweden
	
	• Life expectancy [years, Mean (SD)];-
	  - IAsp = 9.323 (0.162)
	  - HI = 9.176 (0.153)
	  - Difference = + 0.136
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - IAsp = 5.931 (0.107)
	  - HI = 5.854 (0.101)
	  - Difference = + 0.077
	
	• Total costs (direct and indirect costs) (SEK);-
	  - IAsp = 521,538
	  - HI = 532,256
	  - Difference = -10,718
	
	• ICER;-
	  - IAsp dominant.
	
	(Cost saving from both societal and third-party payer perspective)
	
	Spain
	
	• Life expectancy [years, Mean (SD)];-
	  - IAsp = 8.296 (0.116)
	  - HI = 8.195 (0.110)
	  - Difference = + 0.101
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - IAsp = 5.800 (0.083)
	  - HI = 5.720 (0.079)
	  - Difference = + 0.080
	
	• Direct costs (€);-
	  - IAsp = 45,805
	  - HI = 47,187
	  - Difference = 1,382
	
	• ICER;-
	  - IAsp dominant.
	
	(Cost savings from a third-party payer perspective)
	
	Italy
	
	• Life expectancy [years, Mean (SD)];-
	  - IAsp = 9.665 (0.162)
	  - HI = 9.501 (0.157)
	  - Difference = + 0.164
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - IAsp = 6.624 (0.111)
	  - HI = 6.504 (0.109)
	  - Difference = + 0.120
	
	• Direct costs (€);-
	  - IAsp = 54,849
	  - HI = 52,614
	  - Difference = 2,235
	
	• ICER from third-party payer perspective ;-
	  - € 13,627 per life year gained
	  - € 18,597 per QALY gained
	
	Incremental cost-effectiveness scatter plot and acceptability curve:-
	
	• With a willingness to pay threshold of € 30,000 per QALY gained, it would have a 63.7% likelihood of being considered cost-effective.

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Outcome measures/ Effect size (Con't)	**Poland**
	
	• Life expectancy [years, Mean (SD)];-
	  - IAsp = 5.123 (0.119)
	  - HI = 5.095 (0.118)
	  - Difference = + 0.028
	
	• Quality-adjusted life expectancy (QALYs) [Mean (SD)];-
	  - IAsp = 3.055 (0.072)
	  - HI = 3.053 (0.071)
	  - Difference = + 0.003
	
	• Direct costs (€);-
	  - IAsp = 38,070
	  - HI = 37,327
	  - Difference = 743
	
	• ICER from third-party payer perspective ;-
	  - € 22,091 per life year gained
	  - € 290,486 per QALY gained
	
	Incremental cost-effectiveness scatter plot and acceptability curve:-
	
	• With a willingness to pay threshold of € 30,000 per QALY gained, it would have a 37.6% likelihood of being considered cost-effective.
	
	Sensitivity analyses:-
	
	• Results of the one-way sensitivity analyses performed in the Swedish setting revealed that even after change in discount rates and most time horizons, treatment with IAsp would result in improved clinical outcomes and cost-savings versus HI from societal perspective.
	
	• When the improvement in HbA1c associated with IAsp treatment was reduced to the value of that observed for HSI a change of -0.55% from baseline levels, IAsp was projected to be both more expensive and less effective than HI.
	
	• When hypoglycaemic event rates in the IAsp treatment arm were assumed equal to those in the HI arm, IAsp was calculated to be even more effective than HSI, with 0.112 QALYs gained in this scenario versus 0.077 QALYs gained in the base-case.
	
	Cumulative incidence of diabetes-related complications
	
	• In Sweden, patients receiving IAsp had a reduced cumulative incidence of most diabetes-related complications compared with HI. The incidence of end-stage renal disease was reduced by more than 14% and severe vision loss was 7% less frequent for patients receiving IAsp compared to patients receiving HI. The lifetime cumulative incidence of stroke was 2.52% higher for patients receiving IAsp compared to patients receiving HI due to survival paradox, whereby patients on IAsp live longer and are exposed to the risk of stroke for a longer period of time. Similar patterns were observed in spain and Italy, while in Poland whilst a benefir was observed for IAsp versus HI, the projected cumulative incidence of diabetes-related complications was substantially higher than the other countries.
	
	Authors conclusion
	
	IAsp was dominant versus HI in both Sweden and Spain, would be considered cost-effective in Italy with ICER of € 18,597 per QALY gained, but would not be considered cost-effective in Poland.

General comments	Quality assessment (CASP) 1. Yes 2. Yes 3. Yes, but observational study 4. Yes 5. Yes 6. Yes 7. Cost, life expectancy, QALYs, ICER 8. Yes 9. Yes

Evidence Table	**: Economic**
Question	**: Is insulin analogues cost-effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	13. Pratoomsoot C, Smith HT, Kalsekart A, Boyet KS, Arellano J, Valentine WJ. An estimation of long-term clinical and economic benefits of insulin lispro in Type 1 diabetes in the UK. Diabetic Medicine.2009;26:803-814
Study Type / Methods	Economic evaluation The aim of this analysis was to determine the long-term health and economic benefits associated with lispro versus regular human insulin (RHI) in UK type 1 diabetic patients using the previously published and validated CORE Diabetes Model. A literature review designed to capture clinical and benefits associated with lispro and type 1 diabetes mellitus cohort characteristics specific to UK was undertaken. Clinical benefits were derived from Cochrane meta-analysis by Sibenhofer *et al.* 2006. The estimated difference (weighted mean) in glycated haemoglobin (HbA1c) was -0.1% (95% CI; -0.2 to 0.0%) for lispro versus RHI. Severe hypoglycaemia rates for lispro and RHI were 21.8 and 46.1 events per 100 patient years, respectively. Costs and disutilities were accounted for severe hypoglycaemia rates. All costs were accounted in 2007 £UK from a National Health Service (NHS) perspectives. Future costs and clinical benefits were discounted at 3.5% annually. A time horizon of 50 years was used in the base-case analysis. The simulations aimed to capture death of all patients in the simulated cohort (1,000) within 50 years and to project long-term complications with their associated costs and consequently the impact on life expectancy and quality of life over patient lifetimes. Using a non-parametric bootstrapping approach, 1000 mean costs and effect pairs were calculated for each treatment group. Sensitivity analyses were performed around the base-case analysis. Key parameters varied include time horizon, discount rates for costs at 0 and 7% per annum, changes in HbA1c, hypoglycaemia rates and dosage of insulin.
LE	
Number of patients & Patient characteristics	Baseline characteristics of patients in the simulated cohort:-. - Mean age (years) = 37.8 years - 53.4% males - Duration of diabetes (years) = 10.4 years (10.3) - Mean HbA1c(%), mean (SD) = 9.4% (2.10) - BMI (kg/m^2) = 25.6 kg/m^2 (3.1)
Intervention	Insulin lispro
Comparison	Regular Human insulin (RHI)
Length of follow up (if applicable)	

Outcome measures/ Effect size	**Comparison of insulin aspart versus regular human insulin:-** **All costs and clinical outcomes were discounted at 3.5% per annum** • Life expectancy [years, Mean (SD)];- - Lispro = 11.90 (0.179) - RHI = 11.844 (0.167) - Difference = + 0.06 • Quality-adjusted life expectancy (years) [Mean (SD)];- - Lispro = 7.601 (0.117) - RHI = 7.497 (0.107) - Difference = + 0.105 QALYs • Lifetime direct medical costs (£);- - Lispro = 70,576 (1,774) - RHI = 72,529 (1,793 - Difference = -1,953 • ICER (based on life expectancy);- - Insulin lispro dominant • ICER (based on quality-adjusted life expectancy);- - Insulin lispro dominant **Incremental cost-effectiveness scatter plot and acceptability curve:-** • For the base-case scenario, there was a probability of 83.9% that lispro will be cost-effective at a threshold of £ 30,000. **Sensitivity analyses:-** • Revealed that results of the simulation were most sensitive to changes in hypoglycaemic event rates. When no difference in severe hypoglycaemia rates was applied, lispro was associated with a benefit in terms of mean quality-adjusted life expectancy of ≈ 0.034 QALY versus RHI, compared with a benefit of 0.105 QALYs in the base case. The mean saving over a patient's lifetime was ≈ £ 173, assuming no difference in severe hypoglycaemia compared with £ 1, 953 in the base-case. When benefit in severe hypoglycaemia associated with lispro was abolished, the resulting probability that lispro will be cost-effective was 59.1%. Capturing minor hypoglycaemic events in the analysis notably increased the improvement in quality-adjusted life expectancy associated with lispro. In this scenario, lispro treatment was projected to improve mean quality-adjusted life expectancy by approximately 0.355 QALYs versus RHI. • Other sensitivity analyses indicated that lispro treatment regimen remained dominant. **Authors conclusion** Our findings suggest that lispro is likely to improve quality-adjusted life expectancy, reduce frequency of diabetes-related complications and lifetime medical costs compared with RHI.
General comments	Quality assessment (CASP) 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7.Cost, life expectancy QALYs, ICER 8. Yes 9. Yes

Evidence Table : **Economic**

Question : **Is insulin analogues cost-effective for treatment of type 1 diabetes mellitus compared to human insulin?**

Bibliographic citation	14. Reviriego J, Maranes JP, Ricart W, Hudson P, Sacristan JA. Cost of severe hypoglycaemia in patients with type 1 diabetes in Spain and the cost-effectiveness of insulin lispro compared with regular human insulin in preventing severe hypoglycaemia. Inter J Clin Pract. 2008; 62(7):1026-1032
Study Type / Methods	Economic evaluation The objective of this study was to determine the costs of severe hypoglycaemia (SH) in a population of patients with type 1 diabetes mellitus in the Spanish healthcare system and the cost-effectiveness of insulin lispro over regular insulin in preventing SH episodes. A retrospective study of 100 patients in three Spanish health centres was performed. Resource utilisation data were collected only for interventions specifically relating to the hypoglycaemic episode. The direct medical costs determined in the analyses were; costs of hospitalisation, diagnostic tests carried out, costs of treatment administered and other associated costs such as visits to the endocrinologist and re-training in glucose control, transportation and assistance of a care-giver. In addition, indirect costs such as days of lost of productivity were estimated and, where the clinical records did not include sufficient information for this, the patients were interviewed. Cost-effectiveness was calculated using the above costs and the incidence rates of SH for insulin lispro and regular human insulin reported in two randomised , multicentre, 6-month open-label cross-over studies by Anderson *et al.* and Holleman *et al.* The costs of both treatment (insulin lispro and regular human insulin) were calculated adding the cost of the drug to the cost of the episodes of SH in a hypothetic cohort of 100 patients per arm. Since the data were highly skewed, therefore the confidence intervals (CIs) around the mean were calculated using boostrapping with 10,000 simulations. Direct and indirect costs were given as euros of 2005 (€).
LE	
Number of patients & Patient characteristics	Patient demographics (Mean ± SD):-. - Age (years) = 33.22 ± 12.17 - 51% male - 49% female - Duration of diabetes (years) =16.9 ± 10.9 - HbA1c at the time of SH (%, n=46) = 8.12% ± 1.62 - No. of insulin injections per day = 3.37 ± 1.06 - Blood glucose at the time of the SH (mg/dl) = 35.54 ± 8.75 - No. of SH last 2 years = 2.99 ± 3.82

Intervention	Insulin lispro
Comparison	Regular insulin
Length of follow up (if applicable)	
Outcome measures/ Effect size	**Comparison of insulin lispro versus regular insulin:-** • There were 73 (73%) patients who were not aware of the hypoglycaemia and who lost consciousness, while 27 patients had awareness and remained conscious. • In 75% of cases the patient was assisted by a family member during the episode of SH. Glucagon was administered to 40% of the patients and intravenous glucose was given to 27% for the treatment of hypoglycaemia. • The overall mean cost per episode of SH was € 366, comprised of 65.4% direct costs and 34.6% indirect costs. The largest cost was for hospitalisation (€ 183 per episode), which represented 50% of the total costs. • Results from bootstrapping analysis showed a 95% CI of € 124 to € 380 around the mean direct costs and € 211 to € 551 around the mean total cost. • All costs were significantly greater for male patients compared with female patients (total cost, € 454 versus € 274, $P < 0.001$). • Costs were significantly lower for those patients who monitored their blood glucose more than twice per day compared with just twice per day (total cost, € 201 versus € 561, P= 0.011). • Loss of consciousness was significantly associated with greater direct costs and total costs; (total costs, € 460 versus € 113, $P = 0.002$). **Cost-effectiveness of insulin lispro over regular human insulin:-** • Using the study by Anderson *et al.* and Hollerman *et al.* the SH episodes incidence rates for 100 patients per year were 33 and 73 for insulin lispro and 48 and 117 for regular insulin. The additional cost to prevent one episode of SH with insulin lispro over regular insulin ranged from € 277 to insulin lispro dominance. **Authors conclusion** Severe hypoglycaemia has a significant impact on the total cost of diabetes. The use of insulin lispro is associated with reductions in annual costs because the SH and, possibly, the overall effect may be cost neutral or cost saving when total costs are considered. The cost of SH should be included in the analysis of total socio-economic burden of diabetes.
General comments	

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APPENDIX 5

LIST OF EXCLUDED STUDIES

1. Van Avendonk MJP, Rutten GEHM. Insulin Therapy in type 2 diabetes: what is the evidence. Diabetes, Obesity and Metabolism: 2009;11:415-432.

2. Gough SCL. A review of human and analogue insulin trials. Diabetes Research and Clinical Practice.2007; 77:1-15.

3. Chapman TM, Noble S, Goa KL. A review of its use in the management of type 1 and 2 diabetes mellitus.Drugs. 2002;62(13):1945-1981.

4. Wang F, Carabino JM, Vergara CM. Insulin Glargine: A Systematic Review of a Long-Acting Insulin Analogue. Clinical Therapeutics®. 2003;25(6):1541-1577

5. Rosenstock J, Dailey G, Massi-Benedetti M et al. Reduced Hypoglycemia Risk with Insulin Glargine. Diabetes Care. 2005 Apr;25(4):950-955.

6. Fonseca V, Gill J, Zhou R et al. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. Diabetes, Obesity and Metabolism. 200;13(9):814-822

7. Davidson JA, Liebl A, Christiansen JS et al. Risk for Nocturnal Hypoglycemia With Biphasic Insulin Aspart 30 Compared With Biphasic Human Insulin 30 in Adults With Type 2 Diabetes Mellitus: A Meta Analysis. Clinical Therapeutics. 2009;31(8):1641-1651.

8. Manucci E, Monami M, Marchionni N et al. Short-acting insulin analogues vs. regular human insulin in type 2 diabetes: a meta analysis. Diabetes, Obesity and Metabolism.2009;11:53-59.

9. Giugliano D, Maiorina MI, Bellastella G et al. Treatment regimens with insulin analogues and hemoglobin A1c target of <7% in type 2 diabetes: A systematic review. Diabetes Research and Clinical Practice.2011;92:1-10.

10. PontirolliAE, Miele L, Morabito A et al. Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes:systematic review and meta analysis. Diabetes, Obesity and Metabolism.2011;13:1008-1019.

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